

The MPNs as Inflammatory Diseases ?

Perspectives on The Early Interferon Concept

Combination Therapy with Ruxolitinib and Interferon

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Department of Hematology
Roskilde Hospital
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**Mayo Clinic
Scottsdale
February 20-22,2015**

MPNs

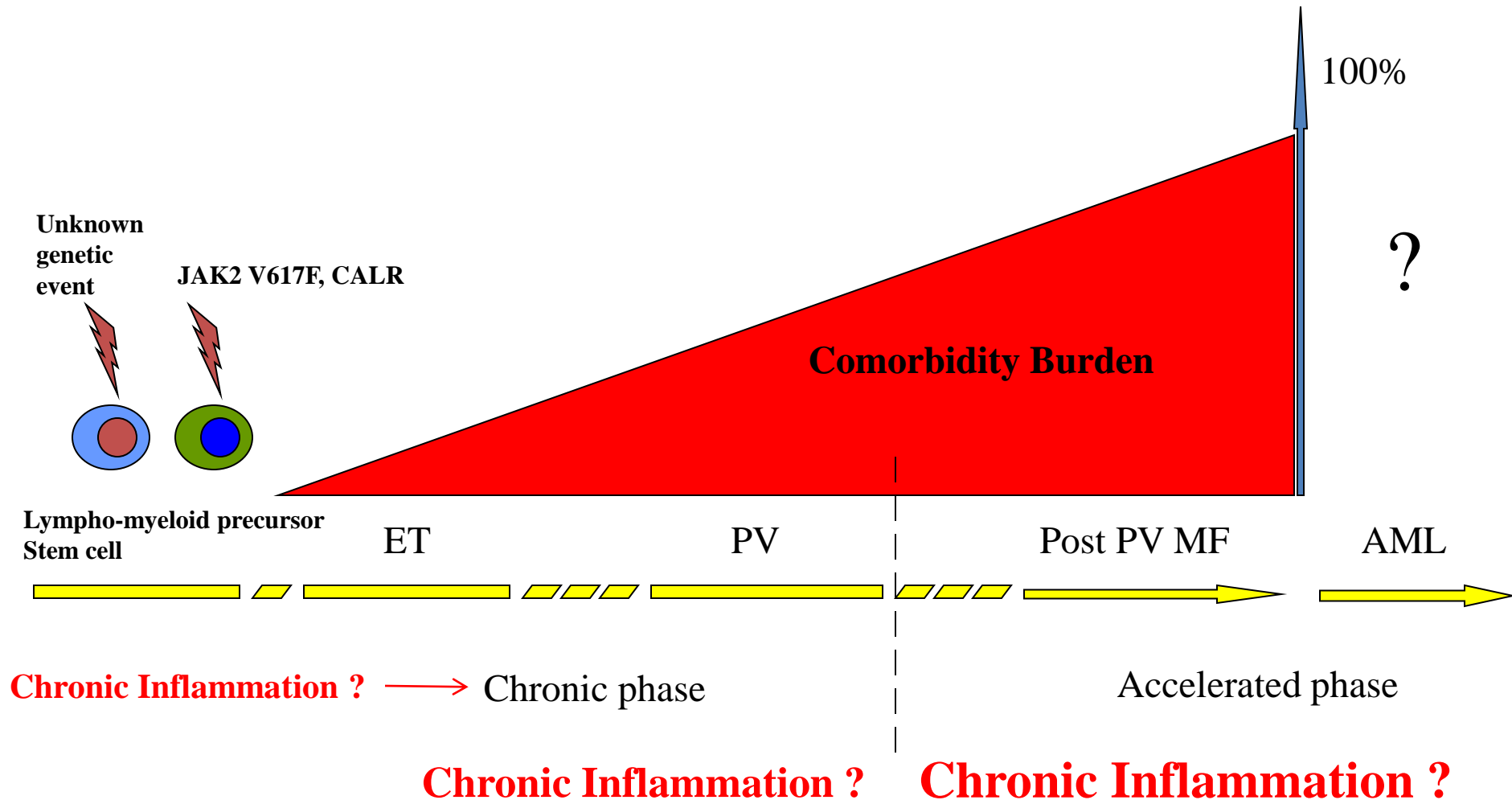
ET – PV - PMF

A Human Inflammation Model ?

A Human Cancer Model ?

Chronic Inflammation – Genomic Instability - Clonal Evolution ?

Tumor Burden and Comorbidity Burden in MPNs



Conclusion I

Inflammation in The Bone Marrow

A microscopic image of bone marrow tissue. The image shows a large, irregular, brownish-yellow mass in the center, which is the bone marrow. It is surrounded by a network of fine, brownish-yellow fibers, likely representing the bone structure. The overall appearance is one of inflammation, with a dense, cellular structure.

The Inflamed Bone Marrow

Cytokine Storm

Bone Marrow Failure

**TNF-Alpha
IL-6 ,IL-8
IL-11, HGF**

**TNF-Alpha
IL-6 ,IL-8
IL-11, HGF**



Conclusion II

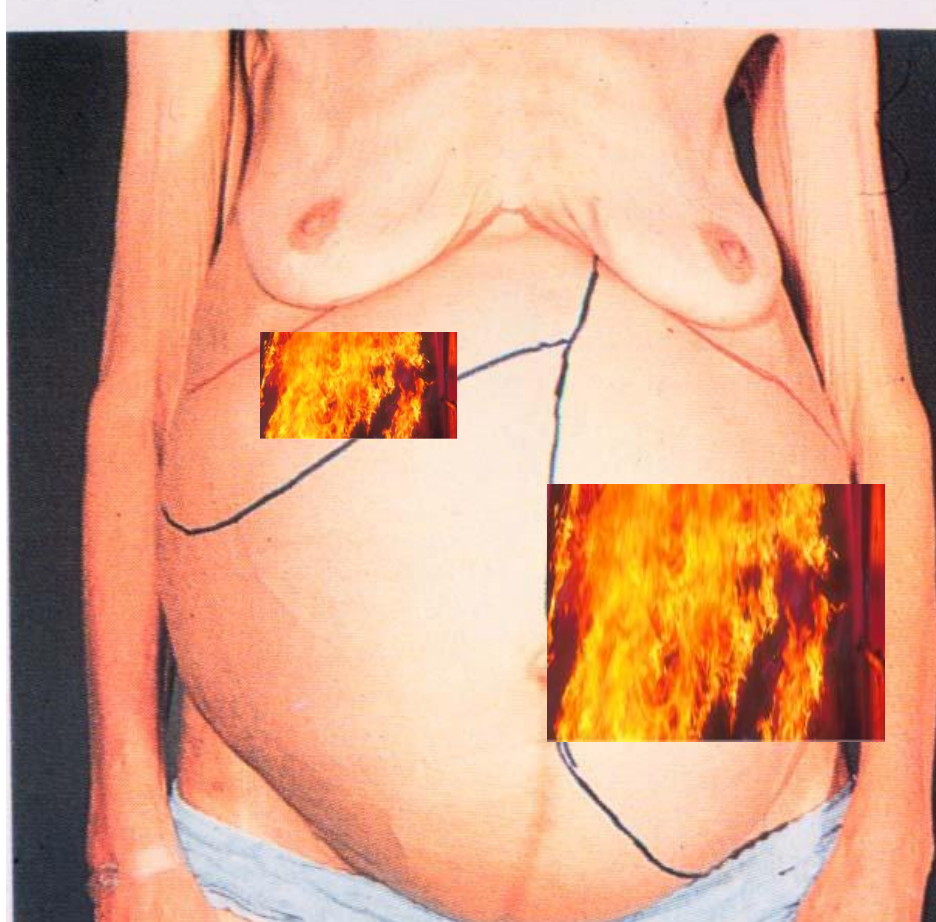
Inflammation in The Circulation



Circulating Leukocyte –Platelet Aggregates
Microcirculatory Disturbances

Conclusion III

Inflammation in The Spleen

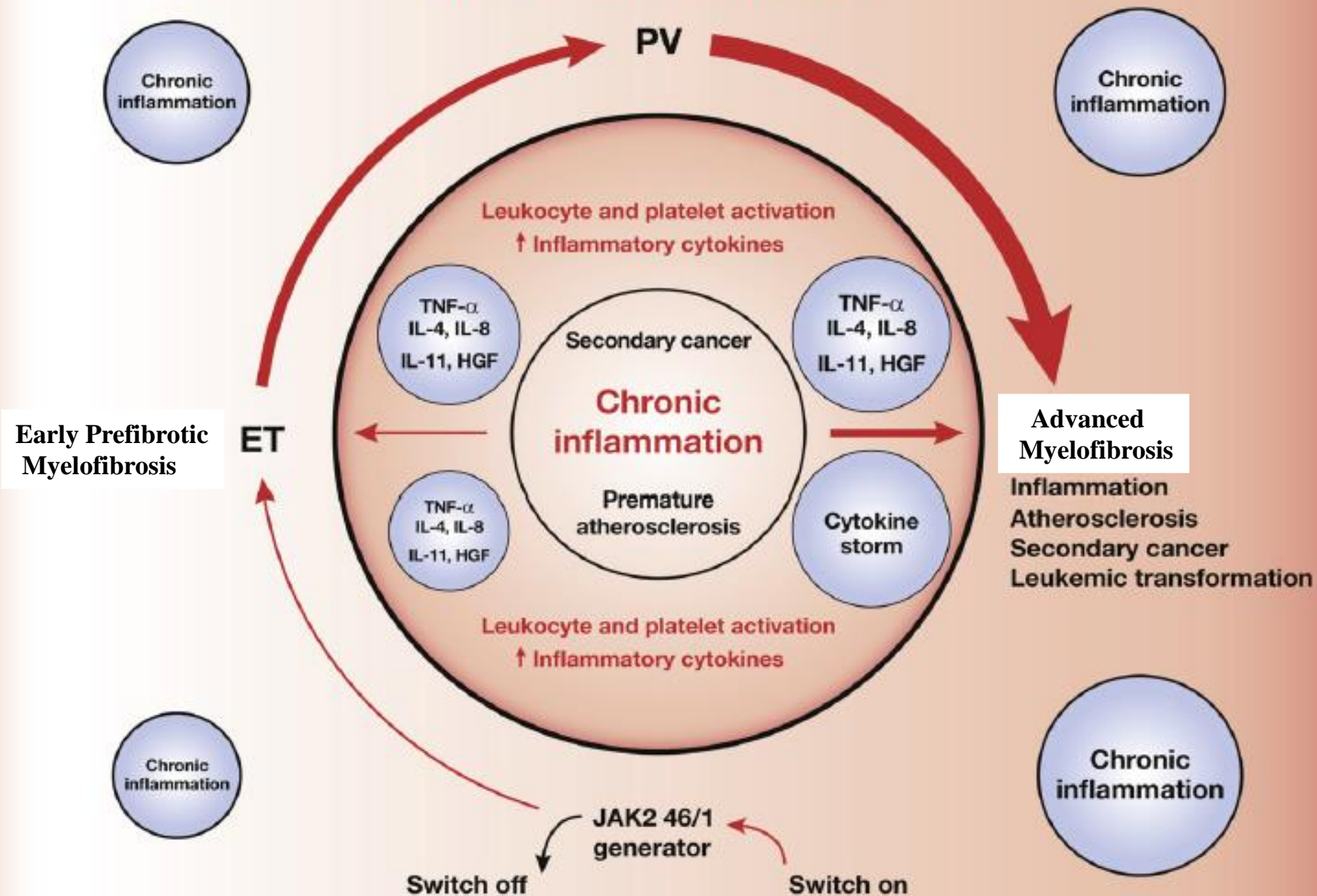


Conclusion IV

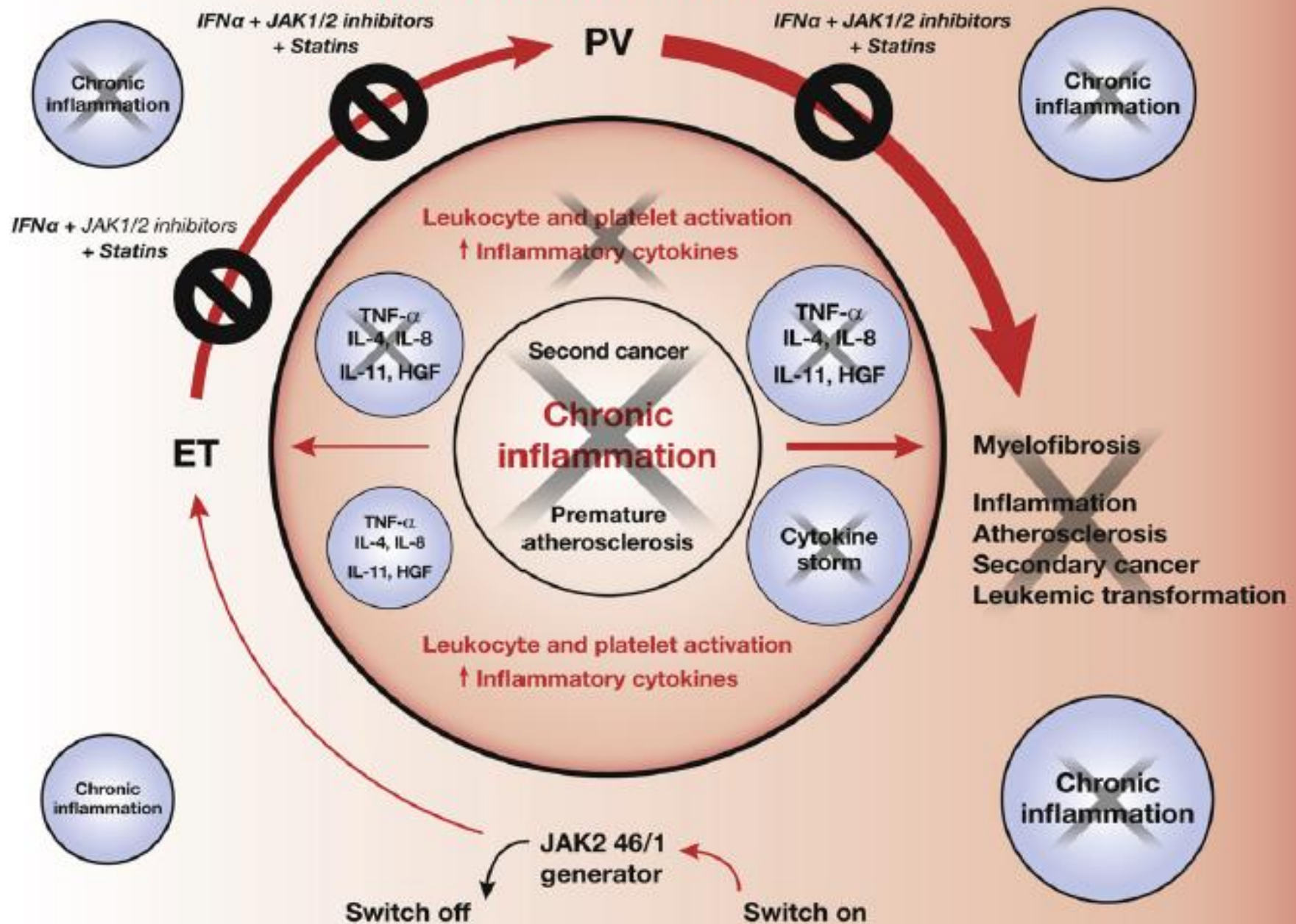
How to Quell the Fire ?

- Early intervention when the chance of quelling the fire is the very best :
- **STOP THE FUEL SUPPLY** : Interferon-alpha
- **ANTIINFLAMMATION** : JAK1-2 inhibitor, statin
HDACi ?

MPN Inflammation Model



MPN Inflammation Model



- **Chronic Inflammation in MPNs –evidence ?**
 - **Epidemiological ?**
 - Histopathological ?
 - Clinical ?
 - Biochemical ?
 - Molecular (eg. gene expression profiling) ?
- Perspectives ?
 - Early Intervention at The Time of Diagnosis ?

Chronic Inflammation in MPNs

The Evidence ?

Epidemiological data

- Anderson LA, Pfeiffer RM, Landgren O et al. Risks of myeloid malignancies in patients with autoimmune conditions. Br J Cancer. 2009;100(5):822-828.
- Kristinsson SY, Bjorkholm M, Hultcrantz M et al. Chronic immune stimulation might act as a trigger for the development of acute myeloid leukemia or myelodysplastic syndromes. J Clin Oncol. 2011; 29(21):2897-2903.
- Kristinsson SY, Landgren O, Samuelsson J et al. Autoimmunity and the risk of myeloproliferative neoplasms. Haematologica. 2010;95(7):1216-1220.

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 - Epidemiological ?
 - **Histopathological ?**
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Chronic Inflammation in MPNs

The Evidence ? Histopathological Data

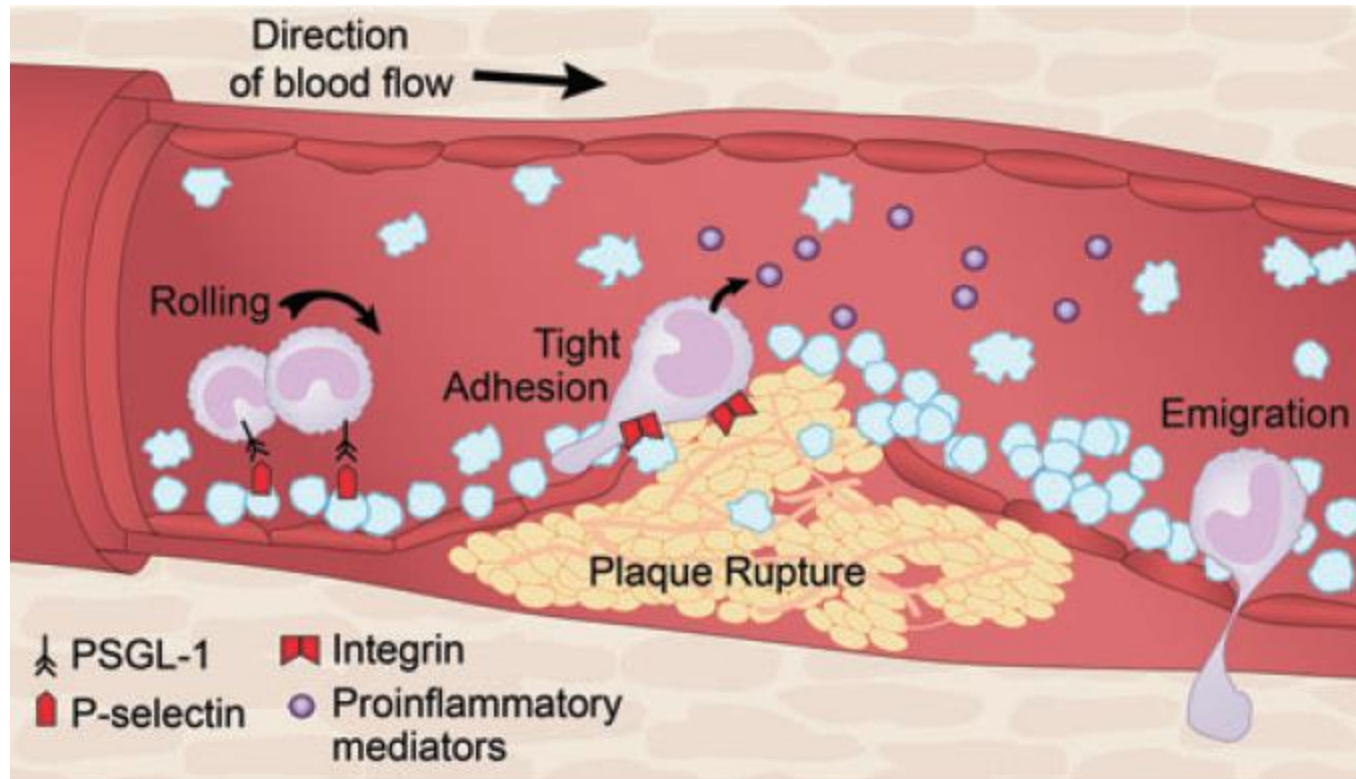
Several reports supporting the participation of immune mechanisms
in the development of bone marrow fibrosis.

- Lennart K, Nagaj K, Scharze EW. In: Videbaek Aa, ed. Polycythaemia vera and myelofibrosis, Clinics in Haematology. London: Saunders, 1975; 80-102.
- Barge J, Slabodsky-Brousse N, Bernard JF. Histoimmunology of myelofibrosis: a study of 100 cases. Biomedicine 1978; 29: 73-75.
- Hunstein W. Experimental myelofibrosis. Clin Haematol 1975; 11:457-478.
- Groopman JE. The pathogenesis of myelofibrosis in myeloproliferative disorders. Ann Intern Med 1980; 92:857-8.

Chronic Inflammation in MPNs

- Epidemiological ?
- Histopathological ?
- **Clinical ?**
- Biochemical ?
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 - Early Intervention at The Time of Diagnosis ?

Platelet–Leukocyte Interactions Link Inflammatory and Thromboembolic events

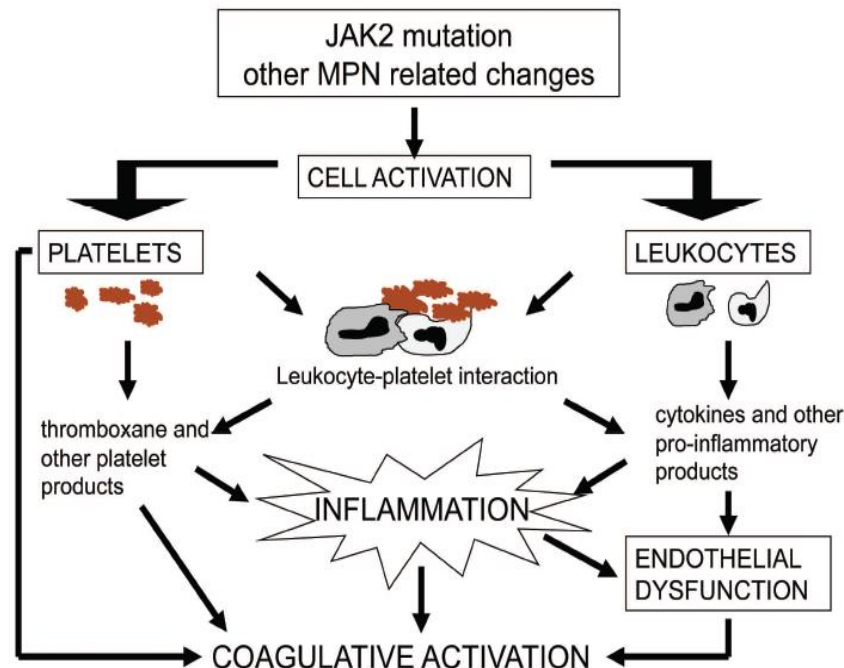


A Link Between Chronic Inflammation and Thrombosis in MPNs ?

Inflammation and thrombosis in essential thrombocythemia and polycythemia vera: different role of C-reactive protein and pentraxin 3

Haematologica 2011;96(2):315-318

Tiziano Barbui,¹ Alessandra Carobbio,¹ Guido Finazzi,¹ Alessandro M. Vannucchi,² Giovanni Barosi,³ Elisabetta Antonioli,² Paola Guglielmelli,² Alessandro Pancrazzi,² Silvia Salmoiraghi,¹ Pio Zilio,⁴ Cosimo Ottomano,⁴ Roberto Marchioli,⁵ Ivan Cuccovillo,⁶ Barbara Bottazzi,⁶ Alberto Mantovani,^{6,7} and Alessandro Rambaldi¹ on behalf of the AGIMM and IIC Investigators



Landolfi R, Di Gennaro L

Editorial: Pathophysiology of thrombosis in myeloproliferative neoplasms

Haematologica 2011;96(2):183-186

A Link Between Chronic Inflammation and (Premature) Atherosclerosis in MPNs

The Evidence ?

- Chronic inflammation has an important role in the development of atherosclerosis
- Chronic inflammatory diseases (eg, rheumatoid arthritis, psoriasis, and systemic lupus erythematosus) are associated with accelerated atherosclerosis (premature atherosclerosis)
- Chronic inflammation has an important impact on the development of premature atherosclerosis in patients with diabetes mellitus
-



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Chronic kidney disease in patients with the Philadelphia-negative chronic myeloproliferative neoplasms



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Chronic inflammation

Hydroxyurea

ABSTRACT

Background: The progression of kidney function and frequency of chronic kidney disease (CKD) in patients with the Philadelphia-negative myeloproliferative neoplasms (MPN) is unknown, although CKD is linked to increased mortality.

Methods: This longitudinal retrospective study evaluates the estimated glomerular filtration rate (eGFR) in 143 MPN patients over a period of 9 years.

Results: 29% of patients had CKD stage 3 or 4 at time of diagnosis. 20% of patients had a rapid annual loss of eGFR ($>3 \text{ mL/min/1.73 m}^2$) and eGFR was negatively correlated to monocyte and neutrophil counts.

Conclusion: Kidney impairment might contribute to the increased mortality observed in MPN patients.

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Previous or Concurrent Autoimmune or Chronic Inflammatory Diseases in MPNs

- Systemic lupus erythematosus
- Progressive systemic sclerosis
- Primary biliary cirrhosis
- Ulcerative colitis, mb. Crohn
- Nephritic syndrome
- Polyarteritis nodosa
- Sjogren syndrome
- Juvenile rheumatoid arthritis
- Psoriasis
- Polymyalgia rheumatica /arteritis temporalis

- **Chronic Inflammation in MPNs –evidence ?**
 - Epidemiological ?
 - Histopathological ?
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 - **Biochemical ?**
 - Molecular (eg. gene expression profiling) ?
- Perspectives ?
 - Early Intervention at The Time of Diagnosis ?

Autoimmunity in Myelofibrosis

Immune-Related Abnormalities

- Antibodies to RBCs (detected in the Coombs test)
- Anti-nuclear and -mitochondrial antibodies (ANA and AMA)
- Rheumatoid factor, lupus-like anti-coagulant
- Low levels of complement
- Increased levels of immune complexes and interleukin-2 soluble receptors (s-IL2R)

Cytokine Profiling Study in Myelofibrosis

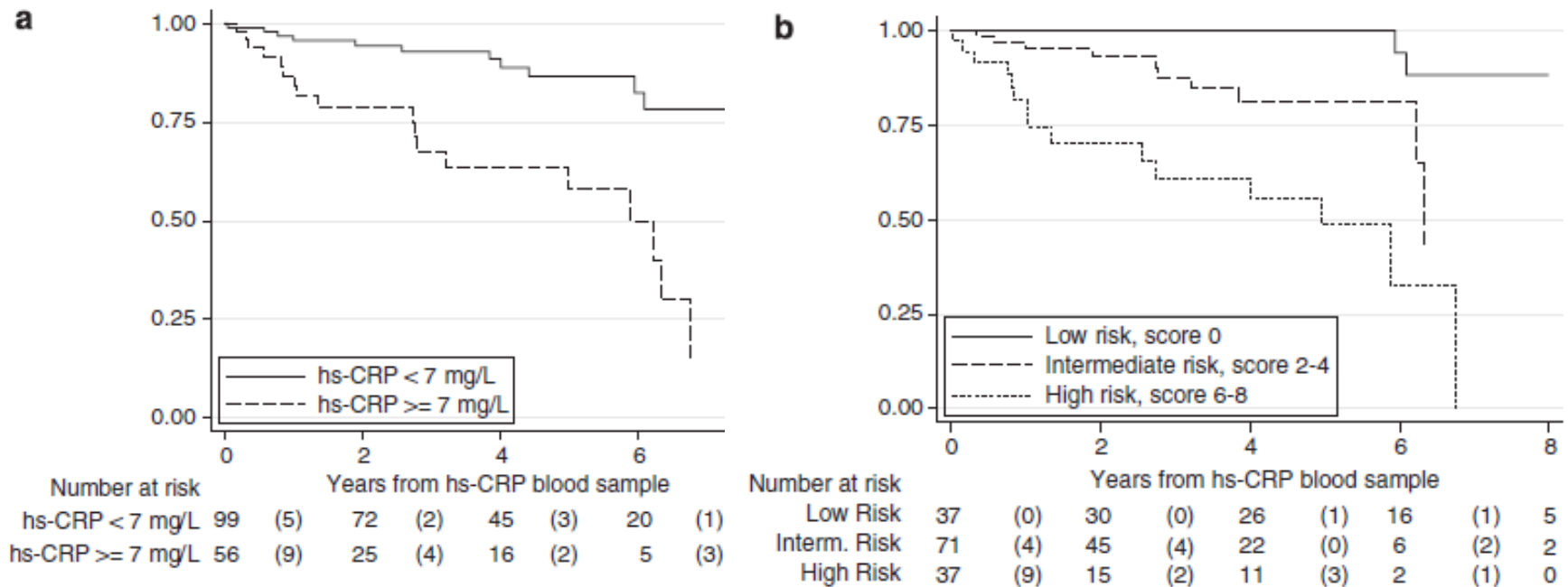
Elevated Cytokines

- IL-1, IL-1RA, IL-2R, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15
- TNF-alpha
- G-CSF
- IFN-alpha
- IFN-inducible protein 10 (IP-10)
- Macrophage inflammatory protein 1(MIP-1)
- Monokine induced by IFN-gamma (MIG)
- Monocyte chemotactic protein 1 (MCP-1)
- Hepatocyte growth factor (HGF),
- Vascular endothelial growth factor (VEGF)

Tefferi A, Vaidya R, Caramazza D, Finke C et al. Circulating Interleukin (IL)-8, IL-2R, IL-12, and IL-15 Levels Are Independently Prognostic in Primary Myelofibrosis: A Comprehensive Cytokine Profiling Study. J Clin Oncol 2011; 29:1356-1363.

Elevated C-reactive protein is associated with shortened leukemia-free survival in patients with myelofibrosis

Barbui T et al *Leukemia* (2013) 27, 2084–2086

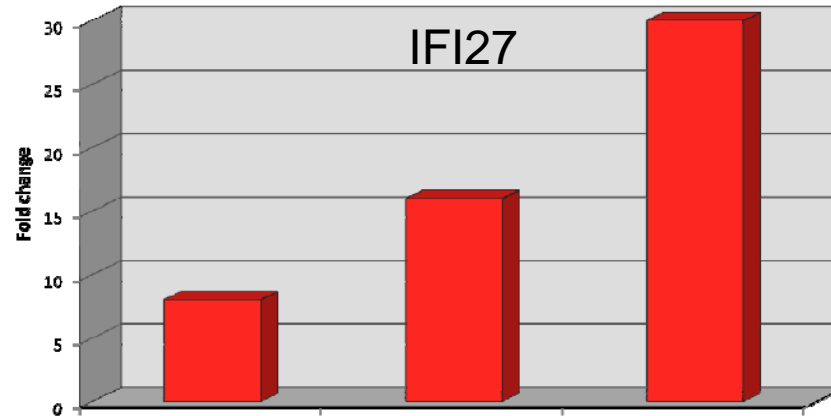


Leukemia-free survival by high (> 7 mg/l) and low (< 7 mg/l) levels of hs-CRP (a)
and according to the new scoring system (b)

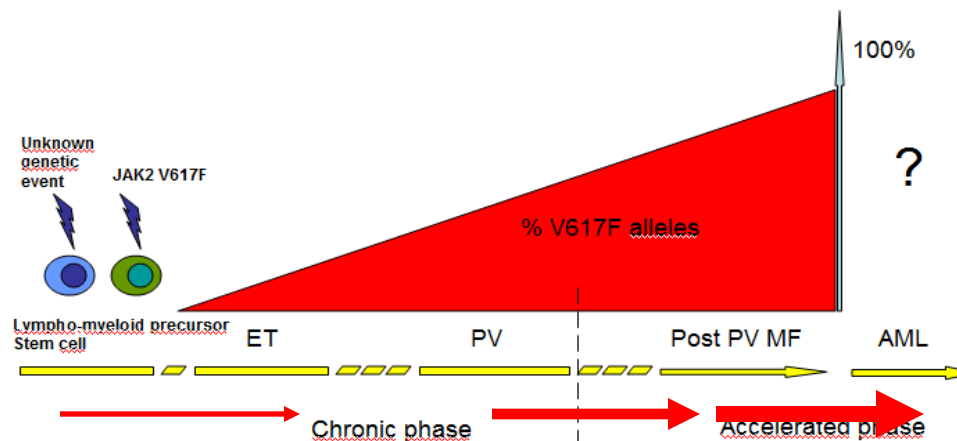
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The Biological Continuum

Chronic Inflammation – Clonal Evolution – Cancer



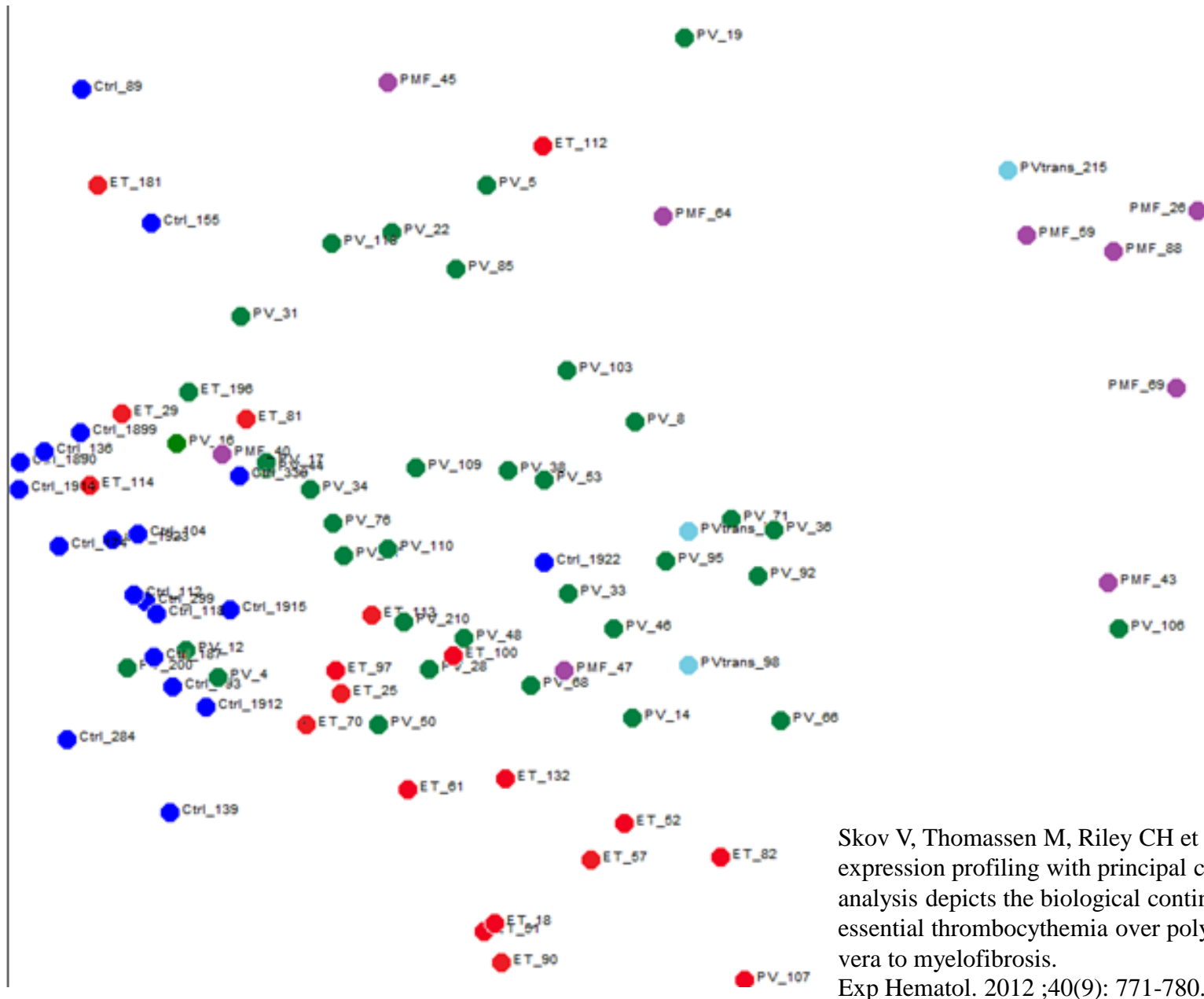
JAK2 V617F positive disorders:
One mutation, three phenotypes – a 2011 model



Chronic Inflammation

Chronic Inflammation

Principal Component Analysis



Skov V, Thomassen M, Riley CH et al. Gene expression profiling with principal component analysis depicts the biological continuum from essential thrombocythemia over polycythemia vera to myelofibrosis. *Exp Hematol.* 2012 ;40(9): 771-780.

Gene Clusters

- Inflammation
- Immune system
- Platelet alpha granule
- Apoptosis

Oxidative Stress

**Reactive Oxygen Species
(ROS)**

Genomic Instability

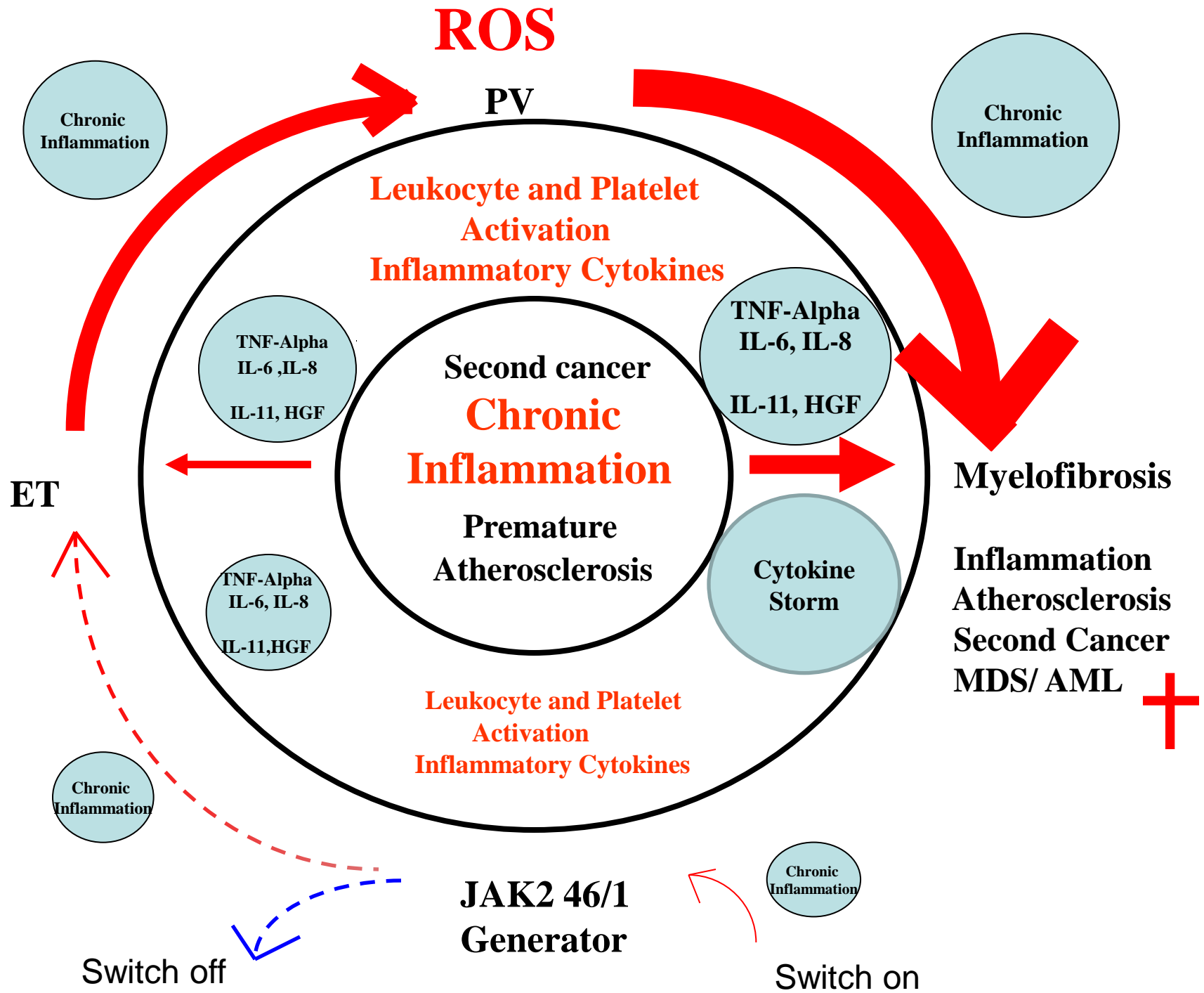
Clonal Evolution

MPNs

A Human Inflammation Model ?

Reactive Oxygen Species

ROS



Review

Chronic inflammation as a promotor of mutagenesis in essential thrombocythemia, polycythemia vera and myelofibrosis. A human inflammation model for cancer development?

Hans Carl Hasselbalch* **Oxidative Stress – ROS-Genomic Instability - Cancer**

Department of Hematology, Roskilde Hospital, University of Copenhagen, Køgevej 7-13, Roskilde, Denmark

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ABSTRACT

The Philadelphia-negative chronic myeloproliferative neoplasms (MPNs) are acquired stem cell neoplasms, in which a stem cell lesion induces an autonomous proliferative advantage. In addition to the JAK2V617 mutation several other mutations have been described. Recently chronic inflammation has been proposed as a trigger and driver of clonal evolution in MPNs. Herein, it is hypothesized that sustained inflammation may elicit the stem cell insult by inducing a state of chronic oxidative stress with elevated levels of reactive oxygen species (ROS) in the bone marrow, thereby creating a high-risk microenvironment for induction of mutations due to the persistent inflammation-induced oxidative damage to DNA in hematopoietic cells. Alterations in the epigenome induced by the chronic inflammatory drive may likely elicit a "epigenetic switch" promoting persistent inflammation. The perspectives of chronic inflammation as the driver of mutagenesis in MPNs is discussed, including early intervention with interferon-alpha2 and potent anti-inflammatory agents (e.g. JAK1-2 inhibitors, histone deacetylase inhibitors, DNA-hypomethylators and statins) to disrupt the self-perpetuating chronic inflammation state and accordingly eliminating a potential trigger of clonal evolution and disease progression with myelofibrotic and leukemic transformation.

ORIGINAL ARTICLE

A role for reactive oxygen species in $JAK2^{V617F}$ myeloproliferative neoplasm progression

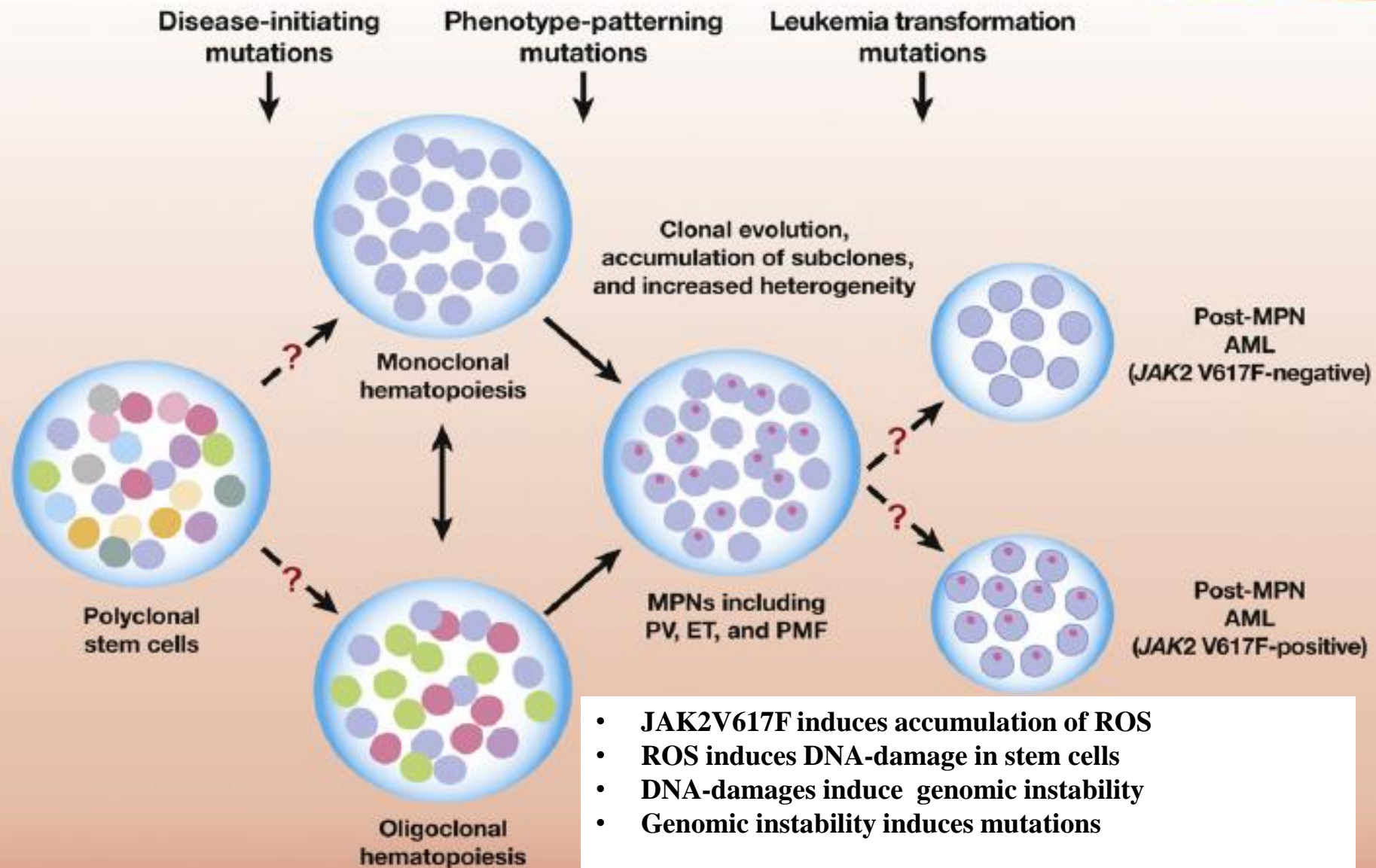
C Marty^{1,2,3}, C Lacout^{1,2,3}, N Droin^{1,2,3}, J-P Le Couédic^{1,2,3}, V Ribrag^{1,2,3}, E Solary^{1,2,3}, W Vainchenker^{1,2,3}, J-L Villeval^{1,2,3} and I Plo^{1,2,3}

Although other mutations may predate the acquisition of the $JAK2^{V617F}$ mutation, the latter is sufficient to drive the disease phenotype observed in BCR-ABL-negative myeloproliferative neoplasms (MPNs). One of the consequences of $JAK2^{V617F}$ is genetic instability that could explain $JAK2^{V617F}$ -mediated MPN progression and heterogeneity. Here, we show that $JAK2^{V617F}$ induces the accumulation of reactive oxygen species (ROS) in the hematopoietic stem cell compartment of a knock-in (KI) mouse model and in patients with $JAK2^{V617F}$ MPNs. $JAK2^{V617F}$ -dependent ROS elevation was partly mediated by an AKT-induced decrease in catalase expression and was accompanied by an increased number of 8-oxo-guanines and DNA double-strand breaks (DSBs). Moreover, there was evidence for a mitotic recombination event in mice resulting in loss of heterozygosity of $Jak2^{V617F}$. Mice engrafted with 30% of $Jak2^{V617F}$ KI bone marrow (BM) cells developed a polycythemia vera-like disorder. Treatment with the anti-oxidant N-acetylcysteine (NAC) substantially restored blood parameters and reduced damages to DNA. Furthermore, NAC induced a marked decrease in splenomegaly with reduction in the frequency of the $Jak2^{V617F}$ -positive hematopoietic progenitors in BM and spleen. Altogether, overproduction of ROS is a mediator of $JAK2^{V617F}$ -induced DNA damages that promote disease progression. Targeting ROS accumulation might prevent the development of $JAK2^{V617F}$ MPNs.

Leukemia advance online publication, 26 April 2013; doi:10.1038/leu.2013.102

Keywords: myeloproliferative neoplasms; $JAK2^{V617F}$; reactive oxygen species; N-acetylcysteine; DNA damages; knock-in mouse model

Chronic Inflammation



- JAK2V617F induces accumulation of ROS
- ROS induces DNA-damage in stem cells
- DNA-damages induce genomic instability
- Genomic instability induces mutations

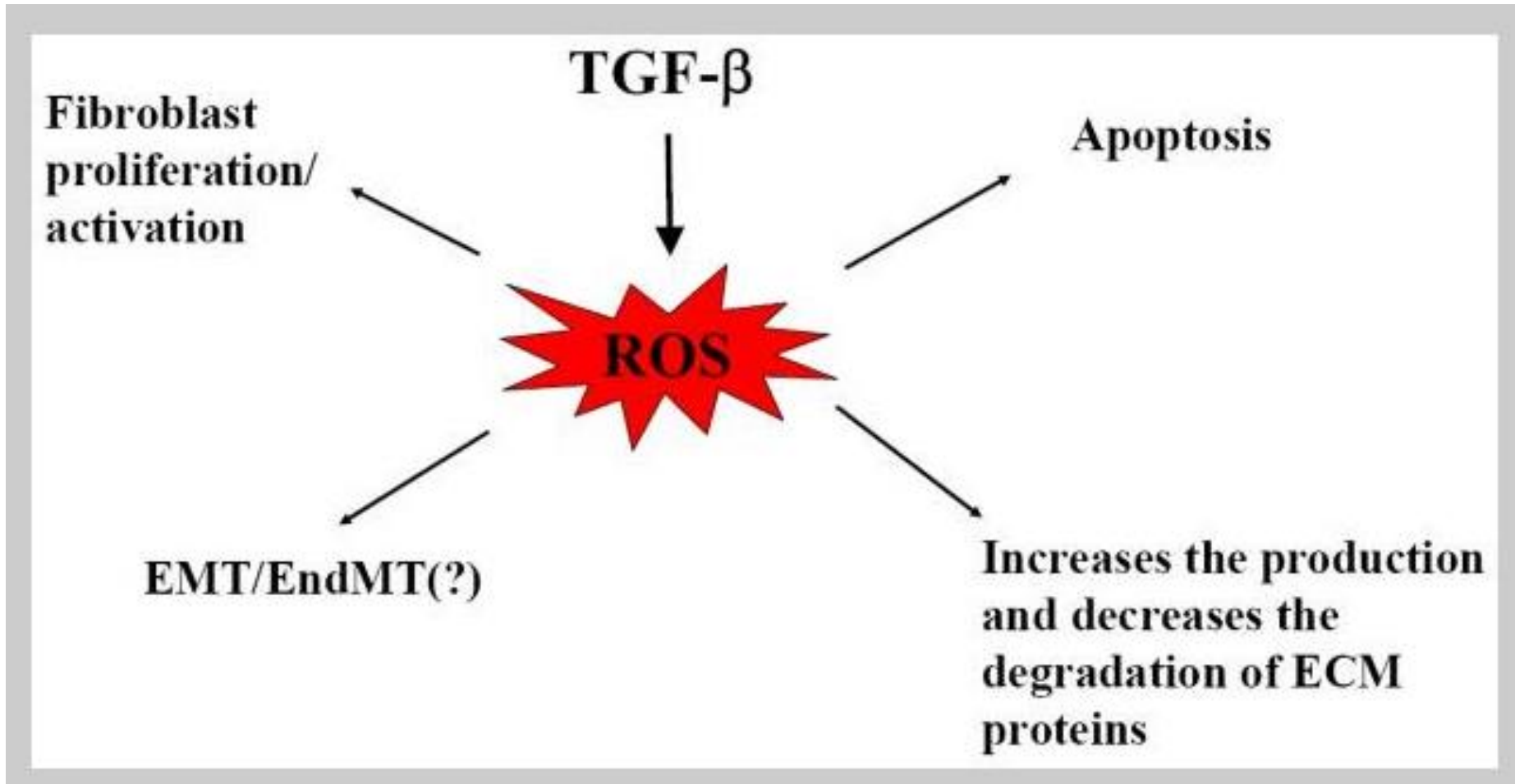
Marty C, Lacout C, Droin N et al. A role for reactive oxygen species in JAK2(V617F) myeloproliferative neoplasm progression. *Leukemia*. 2013 Apr 5.

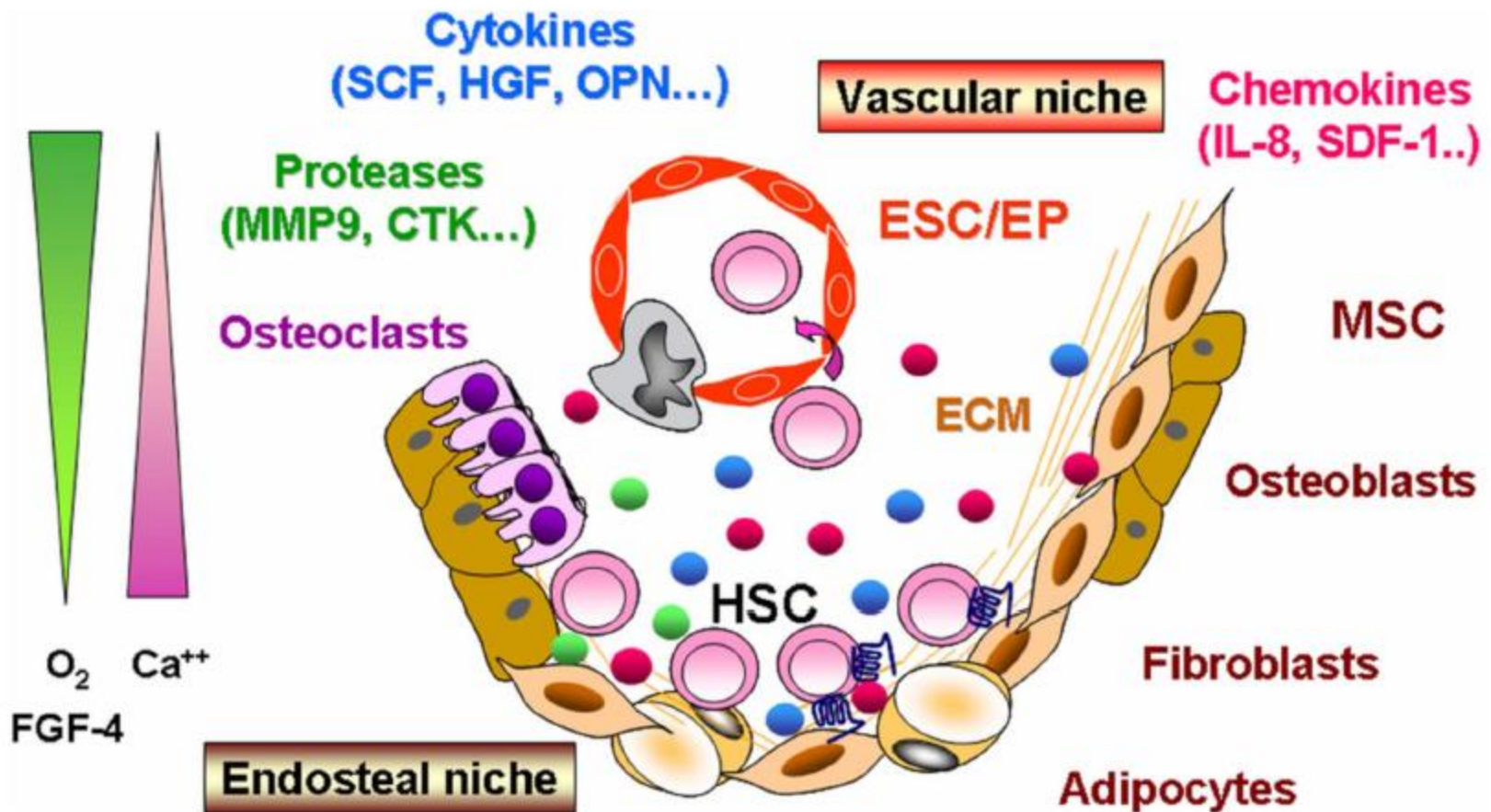
Oxidative Stress

**Reactive Oxygen Species
(ROS)**

Fibrosis ?

ROS Mediate Many of TGF- β 's Fibrogenic Effects





A simplistic model of hematopoietic stem cell niches

Lataillade JJ, Pierre-Louis O, Hasselbalch HC, Uzan G, Jasmin C, Martyré MC, Le Bousse-Kerdilès MC; French INSERM and the European EUMNET Networks on Myelofibrosis. Does primary myelofibrosis involve a defective stem cell niche? From concept to evidence.. Blood. 2008 15;112(8):3026-35.



A simplistic model of hematopoietic stem cell niches

The Inflamed Bone Marrow



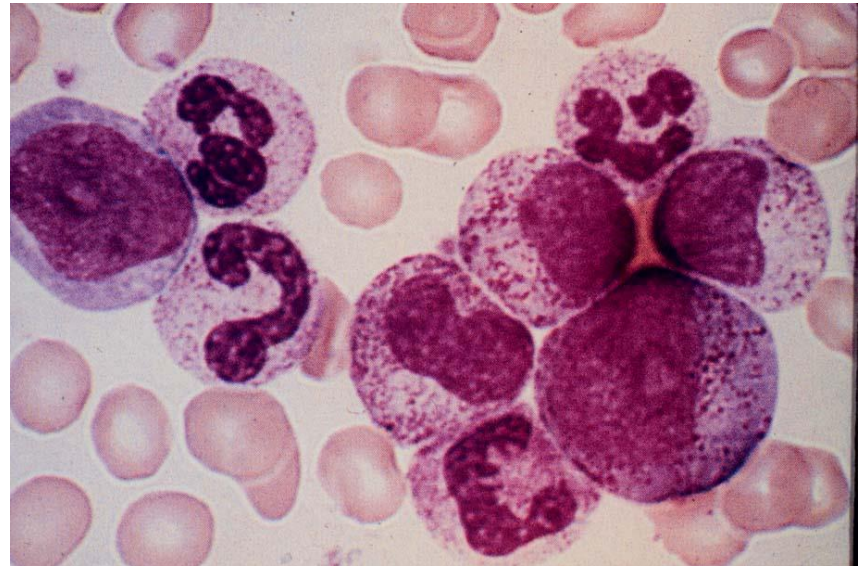
The chicks are flying prematurely (escaping) from the burning nest

Oxidative Stress – ROS Accumulation
Genomic Instability – Mutagenesis - Metastasis

Neutrophil Granules

MMM

- **Mobilization**
- **Metastasis**
- **Myeloid Metaplasia**



Oxidative Stress – ROS Accumulation
Genomic Instability – Mutagenesis - Metastastis

Transcriptional Profiling of Whole Blood Identifies a Unique 5-Gene Signature for Myelofibrosis and Imminent Myelofibrosis Transformation

Hans Carl Hasselbalch^{1*}, Vibe Skov², Thomas Stauffer Larsen³, Mads Thomassen², Caroline Hasselbalch Riley⁴, Morten K. Jensen⁴, Ole Weis Bjerrum⁵, Torben A. Kruse²

1 Department of Hematology, Roskilde Hospital, University of Copenhagen, Roskilde, Denmark, **2** Department of Clinical Genetics, Odense University Hospital, Odense, Denmark, **3** Department of Hematology X, Odense University Hospital, Odense, Denmark, **4** Department of Hematology I, Hærv Hospital, University of Copenhagen, Herlev, Denmark, **5** Department of Hematology I, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Abstract

Identifying a distinct gene signature for myelofibrosis may yield novel information of the genes, which are responsible for progression of essential thrombocythemia and polycythemia vera towards myelofibrosis. We aimed at identifying a simple gene signature – composed of a few genes – which were selectively and highly deregulated in myelofibrosis patients. Gene expression microarray studies have been performed on whole blood from 69 patients with myeloproliferative neoplasms. Amongst the top-20 of the most upregulated genes in PMF compared to controls, we identified 5 genes (DEFA4, ELA2, OLFM4, CTSG, and AZU1), which were highly significantly deregulated in PMF only. None of these genes were significantly regulated in ET and PV patients. However, hierarchical cluster analysis showed that these genes were also highly expressed in a subset of patients with ET (n=1) and PV (n=4) transforming towards myelofibrosis and/or being featured by an aggressive phenotype. We have identified a simple 5-gene signature, which is uniquely and highly significantly deregulated in patients in transitional stages of ET and PV towards myelofibrosis and in patients with PMF only. Some of these genes are considered to be responsible for the derangement of bone marrow stroma in myelofibrosis. Accordingly, this gene-signature may reflect key processes in the pathogenesis and pathophysiology of myelofibrosis development.

Citation: Hasselbalch HC, Skov V, Stauffer Larsen T, Thomassen M, Hasselbalch Riley C, et al. (2014) Transcriptional Profiling of Whole Blood Identifies a Unique 5-Gene Signature for Myelofibrosis and Imminent Myelofibrosis Transformation. PLoS ONE 9(1): e85567. doi:10.1371/journal.pone.0085567

Editor: Andre van Wijnen, University of Massachusetts Medical, United States of America

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Funding: The study has received grants from the The Danish Council for Independent Research | Medical Sciences (<http://fvu.dk/forskning-og-innovation/rad-og-udvalg/det-fre-forskning-rad/det-diff-sundhed-og-sygdom>) The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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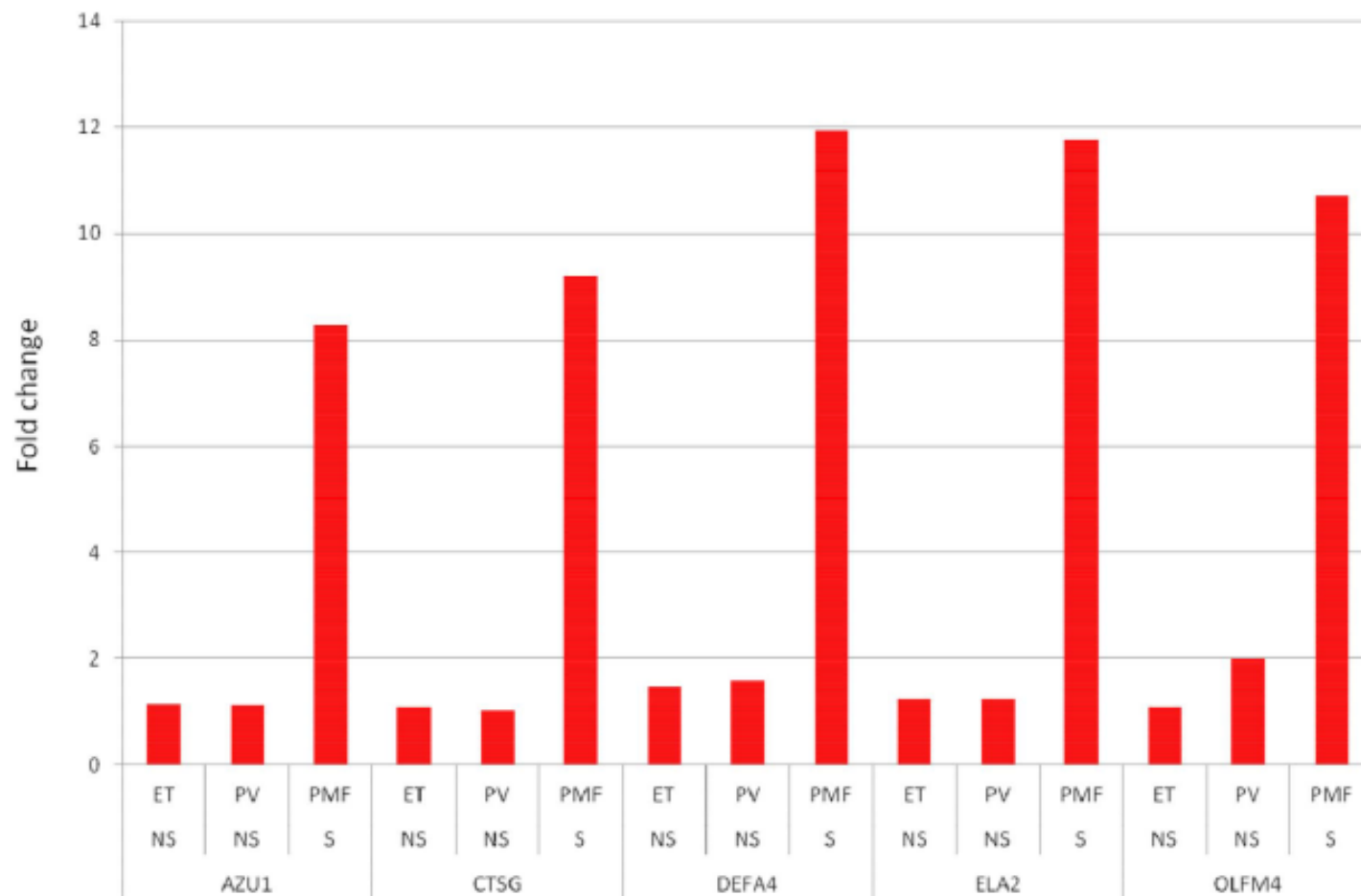


Figure 1. Fold changes for the 5 genes in ET, PV, and PMF compared to control subjects. Patient groups and genes are shown on the x-axis and fold changes on the Y-axis. NS: non-significant; S: significant. All genes FDR<0.05.
doi:10.1371/journal.pone.0085567.g001

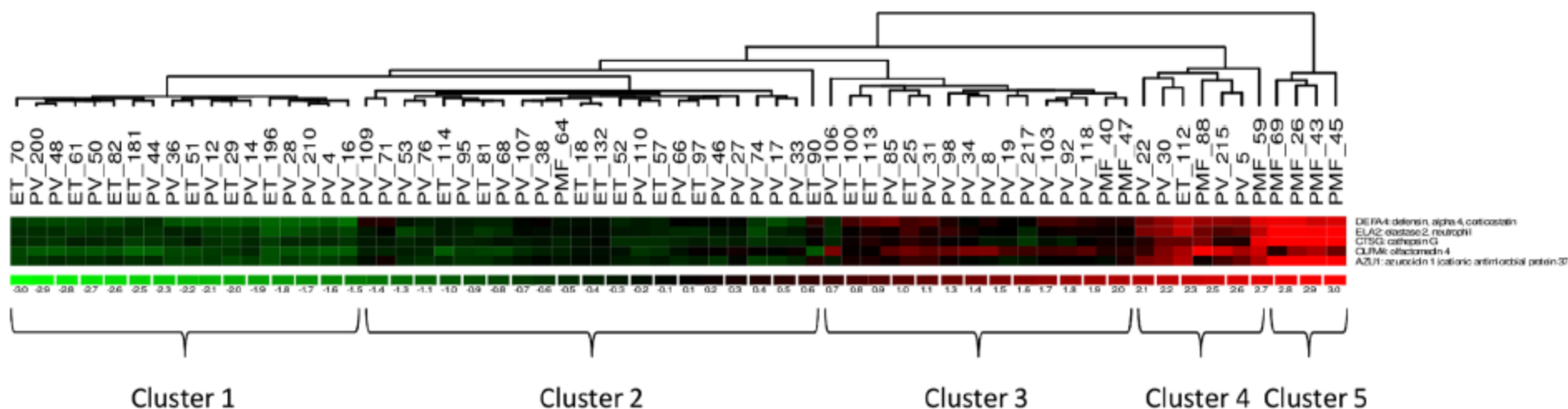
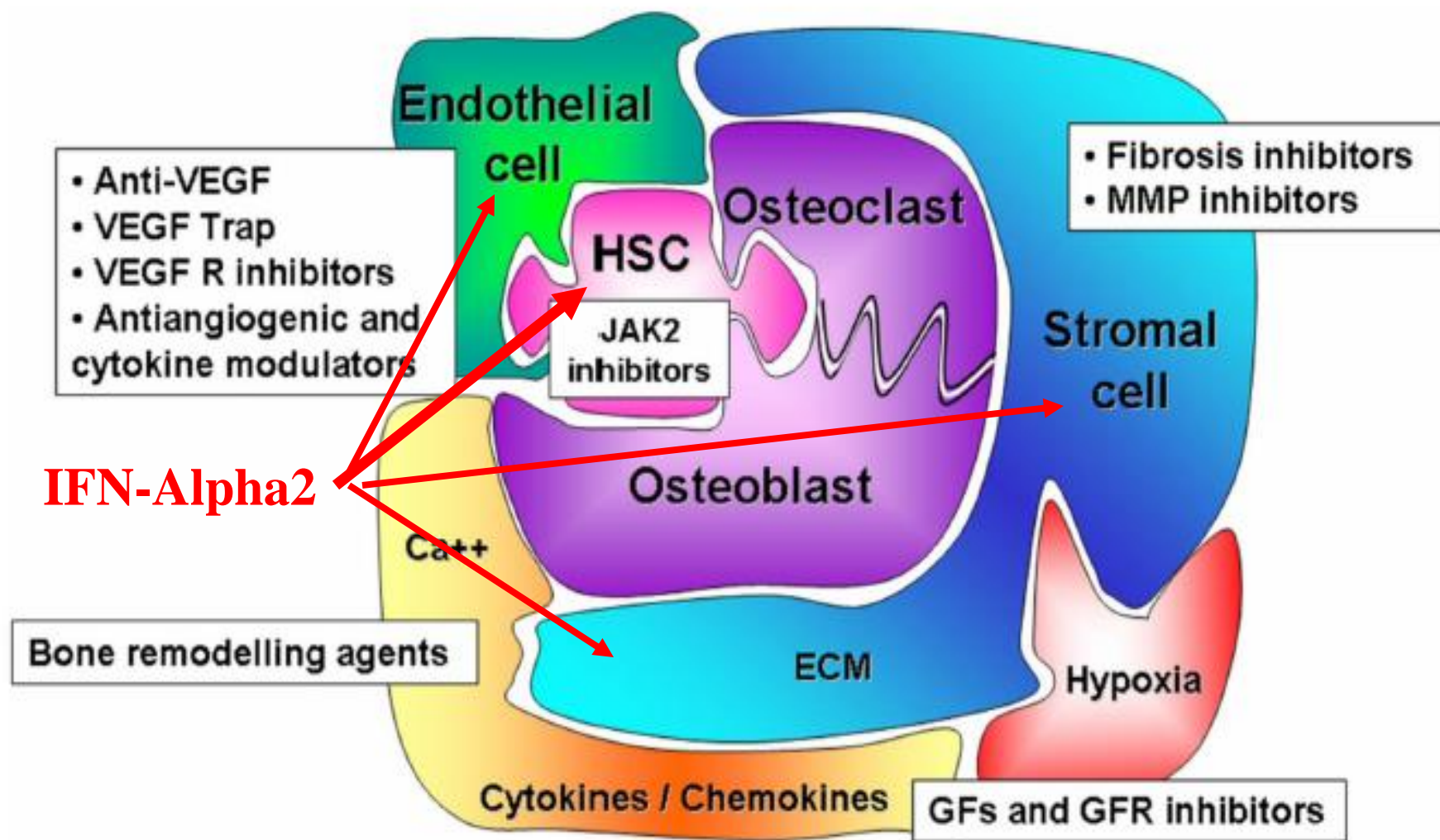


Figure 2. Hierarchical Cluster analysis with euclidean distance in ET, PV and PMF patients. Rows in the heat map represent the five genes DEFA4, ELA2, CTSG, OLFM4, and AZU1, and columns represent patients. The color key ranges from green to red representing standardized expression values of -3.0 to 3.0 . Green indicates low expression, black intermediate expression, and red high expression. Five major clusters can be identified. Cluster 1 (green, low expression), cluster 2 (green-black, low-intermediate expression), cluster 3 (black-red, intermediate expression), cluster 4 (red-black, intermediate-high expression), and cluster 5 (red, high expression). The dendrogram shows the degree of similarity between patients.
doi:10.1371/journal.pone.0085567.g002

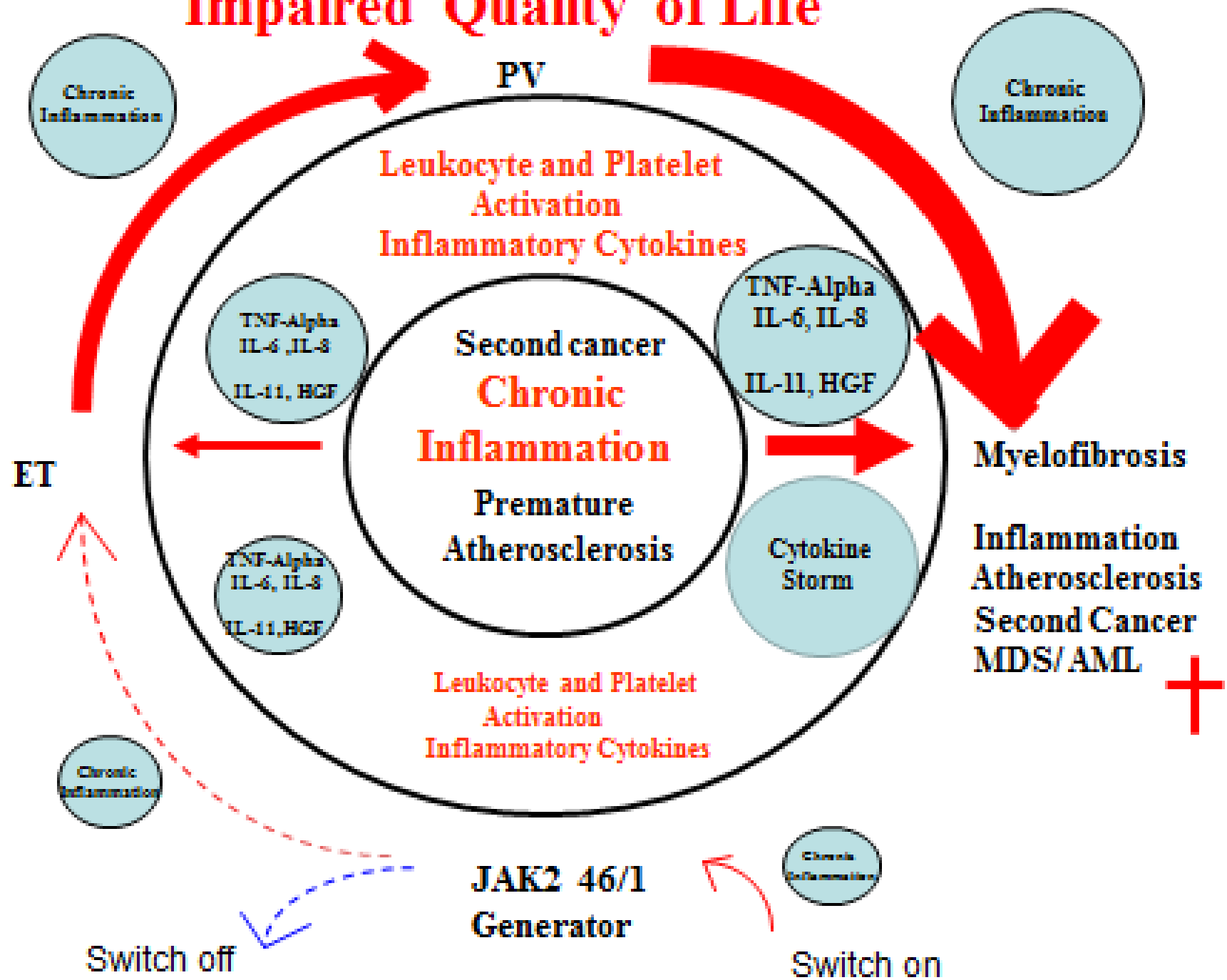


Hematopoietic niches: a new therapeutic target for PMF?

Summary

- MPNs – the Biological Continuum ?
- Chronic Inflammation in MPNs –evidence ?
 - Epidemiological ?
 - Histopathological ?
 - Clinical ?
 - Biochemical ?
 - Molecular (eg. gene expression profiling) ?
- Perspectives ?
 - Early Intervention at The Time of Diagnosis ?

Impaired Quality of Life



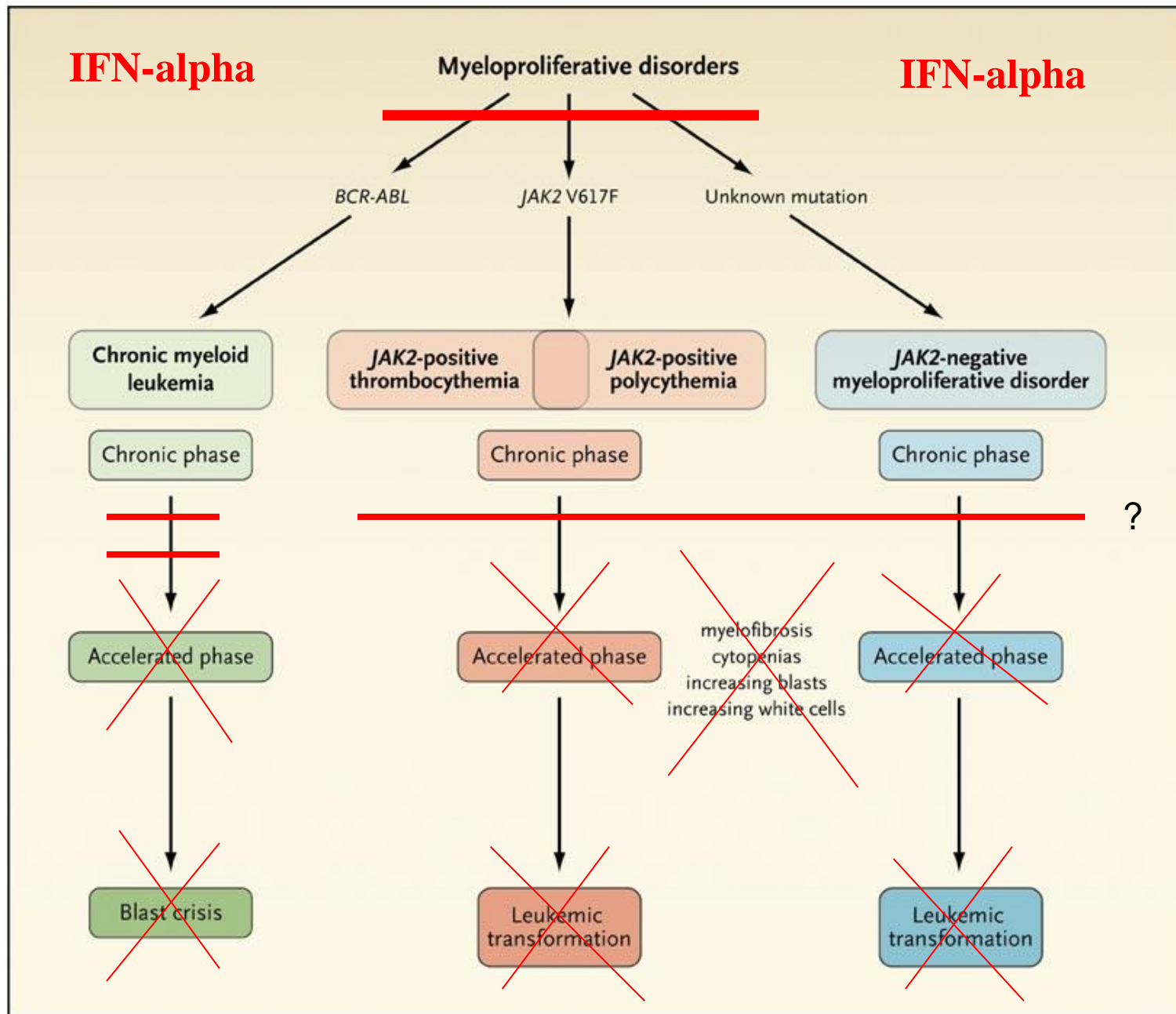
How To Improve Quality of Life in MPNs ?

Inhibit Clonal Evolution and Development of Myelofibrosis

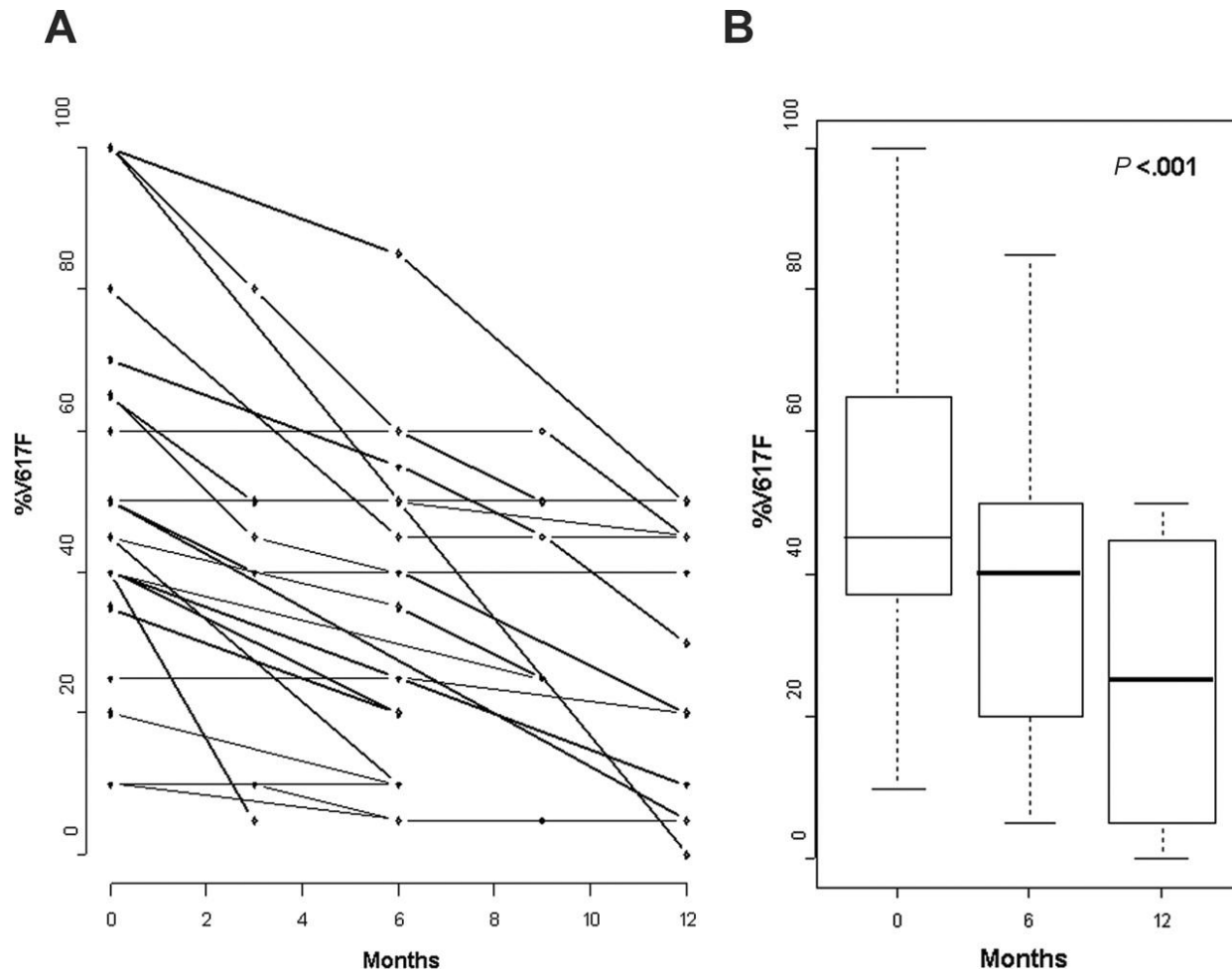
Early Therapeutic Intervention ?

**Interferon-Alpha2
Statins – JAK1-2 Inhibitor – HDACi?**

Stem Cell Wake up Call



Evolution of JAK2-V617F –Mutation during Treatment with Peg-IFN- α -2a



Sustained Molecular Response in Polycythemia Vera Treated with Interferon Alfa-2b

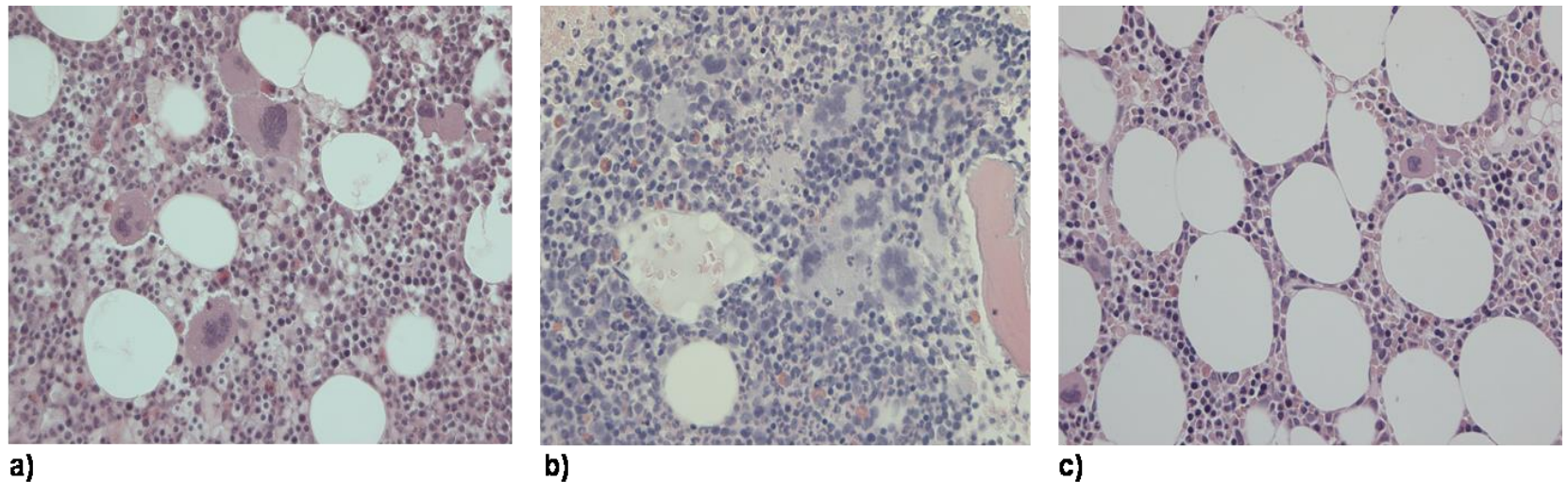


Figure 1: Bone marrow histomorphology from patient 1 at **a) time of diagnosis 1996** and **b) just prior to treatment with IFN alfa-2b**. Both panels demonstrate classical PV features with hyperplasia and clustering of morphological abnormal megakaryocytes. **Panel c) shows the morphologically normal bone marrow from August 2007** (after eight years of treatment with IFN-alfa 2b) with total regression of PV features ([Larsen T et al Ann Hematol 2008; 87: 847–850](#))



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journal homepage: www.elsevier.com/locate/leukres

Long term molecular responses in a cohort of Danish patients with essential thrombocythemia, polycythemia vera and myelofibrosis treated with recombinant interferon alpha

Thomas Stauffer Larsen^{a,*}, Katrine F. Iversen^a, Esben Hansen^b, Anders Bruun Mathiasen^c, Claus Marcher^a, Mikael Frederiksen^d, Herdis Larsen^e, Inge Helleberg^f, Caroline Hasselbalch Riley^g, Ole W. Bjerrum^c, Dorte Rønnov-Jessen^h, Michael Boe Møllerⁱ, Karin de Strickerⁱ, Hanne Vestergaard^a, Hans Carl Hasselbalch^b

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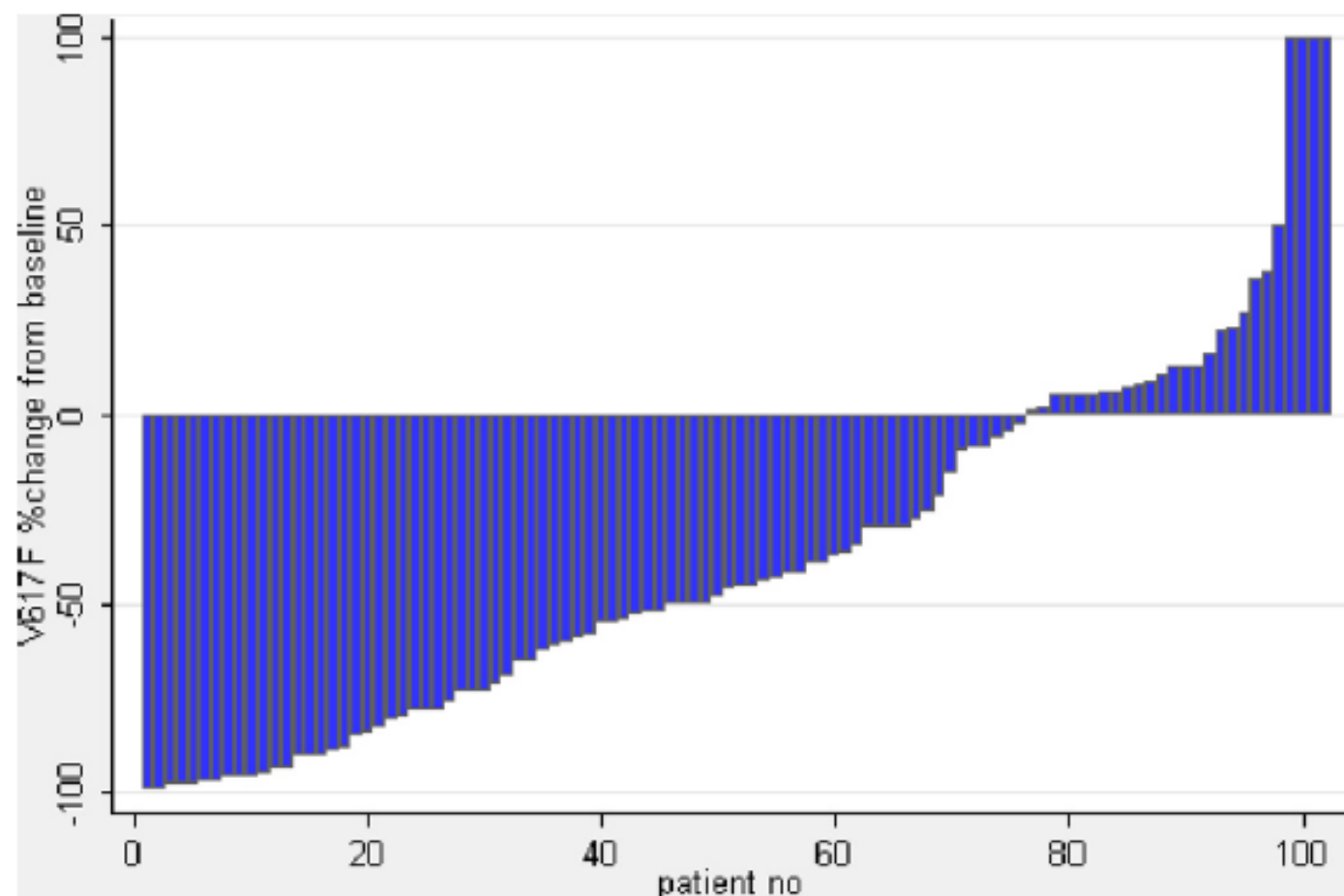


Fig. 1. Waterfall-plot depicting the change from baseline in JAK2 V617F mutant allele burden in the 102 individual patients with a median follow-up of 42 months (range 12–146 months). For the 4 patients with a 100% increase the bars are modified to fit the 100% y-scale. The patients had a 138% (from 5% to 17%, PV), 200% (from 10% to 30%, PV), 225% (from 12% to 35%, ET) and 240% (from 5% to 17%, ET) increase, respectively.

Minimal Residual Disease after Long-term Interferon-Alpha2 treatment in
Essential Thrombocytemia and Polycythemia Vera.
A Report on Hematological, Molecular, and Histomorphological Response
Patterns in Eleven Patients.

Cecilie Utke Rank¹, Ole Weis Bjerrum², Thomas Stauffer Larsen³, Lasse Kjær¹, Karin de Stricker⁴, Caroline Hasselbalch Riley⁵, Hans Carl Hasselbalch¹

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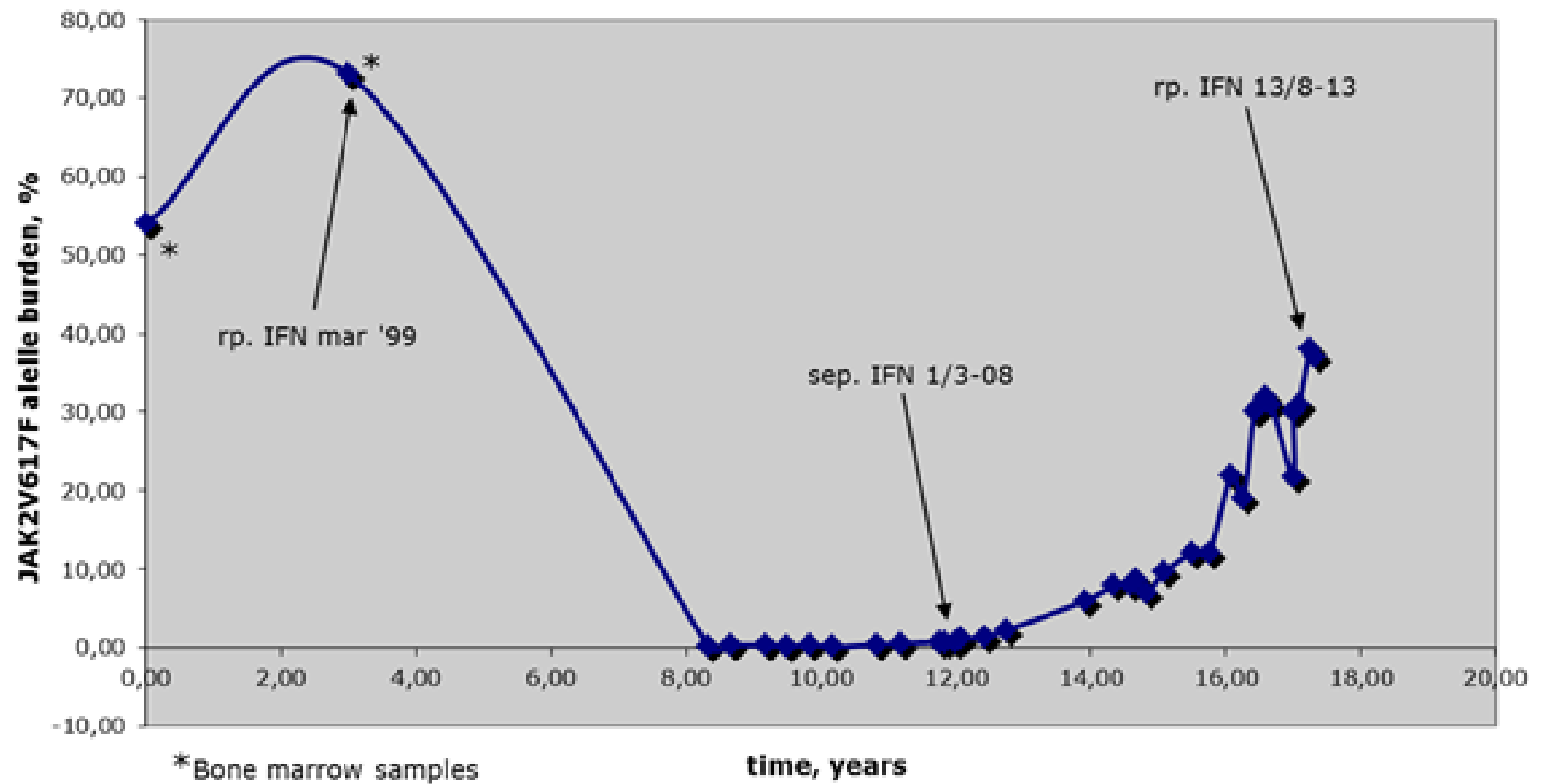
2 Department of Hematology, Rigshospitalet, University of Copenhagen

3 Department of Hematology, Odense University Hospital

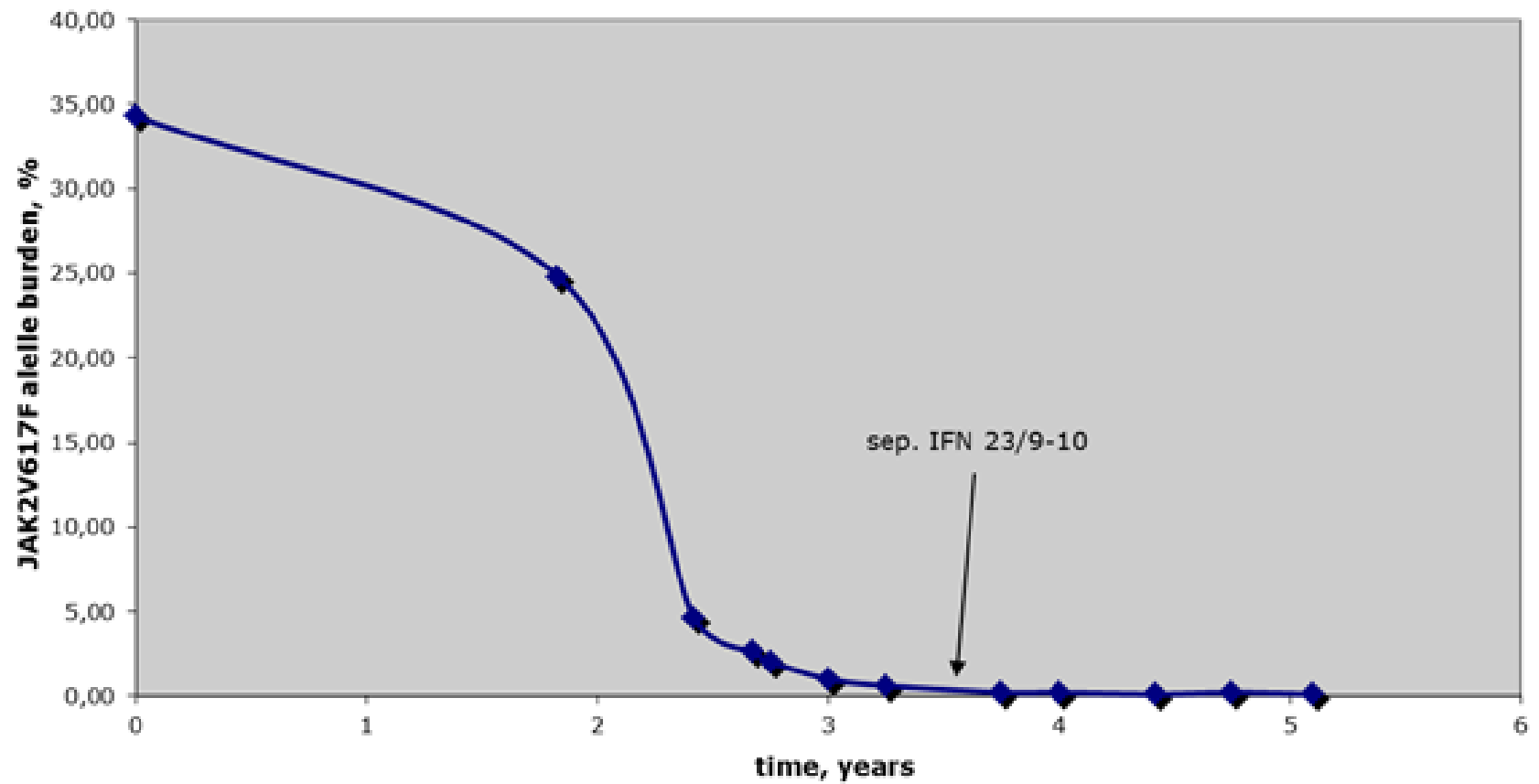
4 Department of Pathology, Odense University Hospital

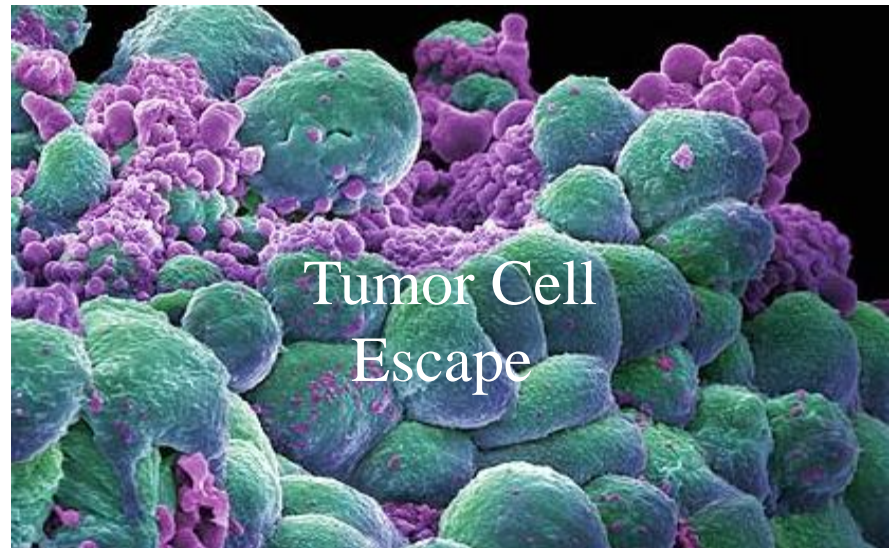
5 Department of Hematology, Herlev Hospital, University of Copenhagen

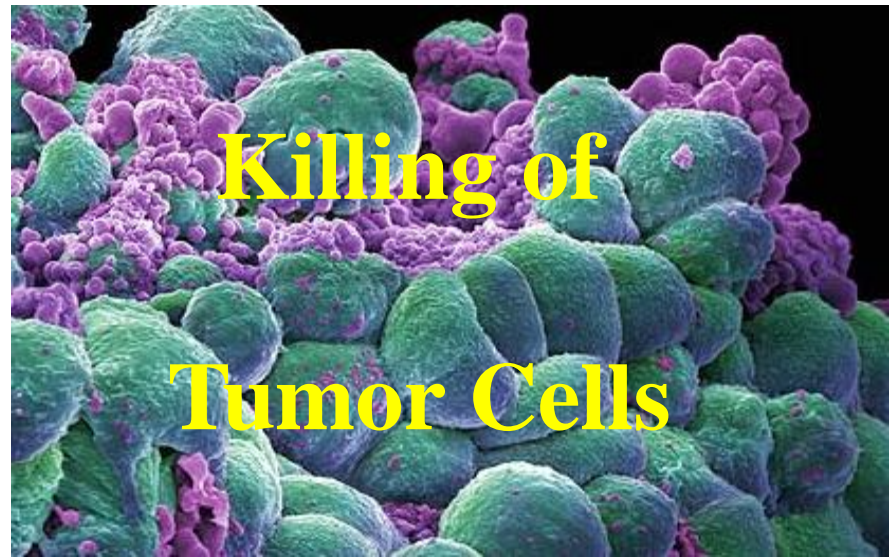
**Patient 2: Serial Measurements of JAK2V617F
during and after discontinuation of interferon-alpha treatment**



**Patient 9: Serial Measurements of JAK2V617F
during and after discontinuation of interferon-alpha treatment**







Two Different Scenarios

No Access IFN-alpha2

- "Do no harm"
- Risk stratification
- Normal blood counts
- ~~Cytogenetic remission~~
- ~~Molecular remission~~
- ~~Normal bone marrow~~
- ~~Minimal residual disease~~

Access IFN-alpha2

- ~~"Do no harm"~~
- ~~Risk Stratification~~
- Normal blood counts
- Cytogenetic remission
- Molecular remission
- Normal bone marrow
- Minimal residual disease

Two Different Scenarios

No Access IFN-alpha2

- STOP HU

~~Sustained~~

- ~~Complete HR~~
- ~~Molecular remission~~
- ~~Normal bone marrow~~
- ~~Minimal residual disease~~

Access IFN-alpha2

- STOP IFN

Sustained

- Complete HR
- Molecular remission
- Normal bone marrow
- Minimal residual disease

A subset of patients

Two Different Scenarios

No Access IFN-alpha2

- **HU (>10 yrs)**
-
- Risk of
- Skin cancer ?
- MDS/AML ?
- Second cancer ?

Access IFN-alpha2

- **IFN-alpha2**
-
- Risk of
- ~~Skin cancer ?~~
- ~~MDS/AML ?~~
- ~~Second cancer ?~~

Rationale for Early Intervention IFN-alpha2

- ✓ Major /Complete Molecular Remissions after Long-Term Treatment (> 3 -5 years)
- ✓ Sustained Molecular Remissions after Discontinuation of IFN-alpha2
- ✓ Minimal Residual Disease
- ✓ JAK2V617F ET the Early Phase of PV in a Subset of Patients
- ✓ “ET “ Early Phase of Myelofibrosis in a Subset of Patients
- ✓ MPNs Associated with an Increased Risk of Second Cancer
- ✓ IFN-alpha2 Enhancer of ”Tumor Immune Surveillance”
- ✓ Early Intervention with IFN-alpha2 Decreases the Risk of Second Cancer ?
- ✓ JAK2V617F Tumor Promoter ?

Chronic myeloproliferative neoplasms and subsequent cancer risk: a Danish population-based cohort study

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Patients with chronic myeloproliferative neoplasms, including essential thrombocythemia (ET), polycythemia vera (PV), and chronic myeloid leukemia (CML), are at increased risk of new hematologic malignancies, but their risk of nonhematologic malignancies remains unknown. In the present study, we assessed the risk of both types of malignancies after an ET, PV, or CML diagnosis. We linked 2 population-based nationwide registries, the Danish National Registry of Patients, cover-

ing all Danish hospitals and the Danish Cancer Registry, and assessed subsequent cancer risk in a cohort of all 7229 patients diagnosed with a chronic myeloproliferative neoplasm during 1977-2008. We compared the incidence of subsequent cancer in this cohort with that expected on the basis of cancer incidence in the general population (standardized incidence ratio). Overall, ET, PV, and CML patients were at increased risk of developing both new hematologic and

nonhematologic cancers. The standardized incidence ratio for developing a nonhematologic cancer was 1.2 (95% confidence interval [95% CI]: 1.0-1.4) for patients with ET, 1.4 (95% CI: 1.3-1.5) for patients with PV, and 1.6 (95% CI: 1.3-2.0) for patients with CML. We conclude that patients with chronic myeloproliferative neoplasms are at increased risk of developing a new malignant disease. (*Blood*. 2011;118(25):6515-6520)

ORIGINAL ARTICLE

Increased incidence of another cancer in myeloproliferative neoplasms patients at the time of diagnosis

Helna Pettersson¹, Håvar Knutsen², Erik Holmberg³, Björn Andréasson^{1,4}

¹Hematology section, Uddevalla, NU hospital group, Uddevalla, Sweden; ²Hematology section, Ullevål Hospital, Oslo, Norway; ³Regional Oncology Center, Göteborg; ⁴Section of Hematology and Coagulation, Sahlgrenska University Hospital, Göteborg, Sweden

Abstract

Several studies have reported an increased incidence of coexistent cancer in patients with myeloproliferative neoplasms (MPN), and myelosuppressive treatment has been speculated to be one of the causes. In this study, we have concentrated on malignancies diagnosed before the MPN diagnosis to eliminate the possible influence of MPN treatment. The patients were recruited from the Swedish and Norwegian cancer registries. One thousand seven hundred and 45 patients from the Swedish MPN Quality Registry and 468 patients from the Norwegian National Cancer Registry were included in this study covering a 3-yr period. The results show that primary concurrent cancer is higher among patients with MPN compared to the general population. When pooled together, the Swedish and the Norwegian cohort showed increased prevalence of all types of cancer in general compared with the general population, standard prevalence ratio (SPR) of 1.20 (95% CI 1.07–1.34). Significantly high SPRs were reached for skin malignant melanoma [1.89 (95% CI 1.33–2.62)], prostate cancer [1.39 (95% CI 1.11–1.71)], and hematologic cancer [1.49 (95% CI 1.00–2.12)]. In the polycythemia vera group, the risk of having prior malignant melanoma of the skin was significant, with an SPR of 2.20 (95% CI 1.17–3.77). For patients with essential thrombocythemia and primary myelofibrosis, no significant risks were found. Coexisting cancers have a high impact on the treatment strategies of MPN, as it narrows down the treatment options. Chronic inflammation, as a common denominator of MPN with other cancers, can catalyze each other's existence and progression.

Key words myeloproliferative neoplasm; polycythemia vera; essential thrombocythemia; primary myelofibrosis; cancer

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Impaired Tumor Immune Surveillance ?

Chronic Inflammation ?

Immune Deregulation ?

ORIGINAL ARTICLE: RESEARCH

Whole blood transcriptional profiling reveals significant down-regulation of human leukocyte antigen class I and II genes in essential thrombocythemia, polycythemia vera and myelofibrosis

Vibe Skov¹, Caroline Hasselbalch Riley², Mads Thomassen¹, Thomas Stauffer Larsen³, Morten K. Jensen², Ole Weis Bjerrum⁴, Torben A. Kruse¹ & Hans Carl Hasselbalch⁵

Perspectives :

- Down-regulation of HLA-genes is a "tumor-escape mechanism" by which tumor cells escape the attack from potent immune cells e.g. cytotoxic T cells and NK-cells)
- Interferon-alpha2 potently upregulate HLA-genes on tumor cells thereby rendering them accessible for tumor killing by IFN-alpha2
- Early treatment with IFN to enhance tumor cell killing

Improvement of Tumor Immune Surveillance

Interferon- α 2
From the Time of Diagnosis

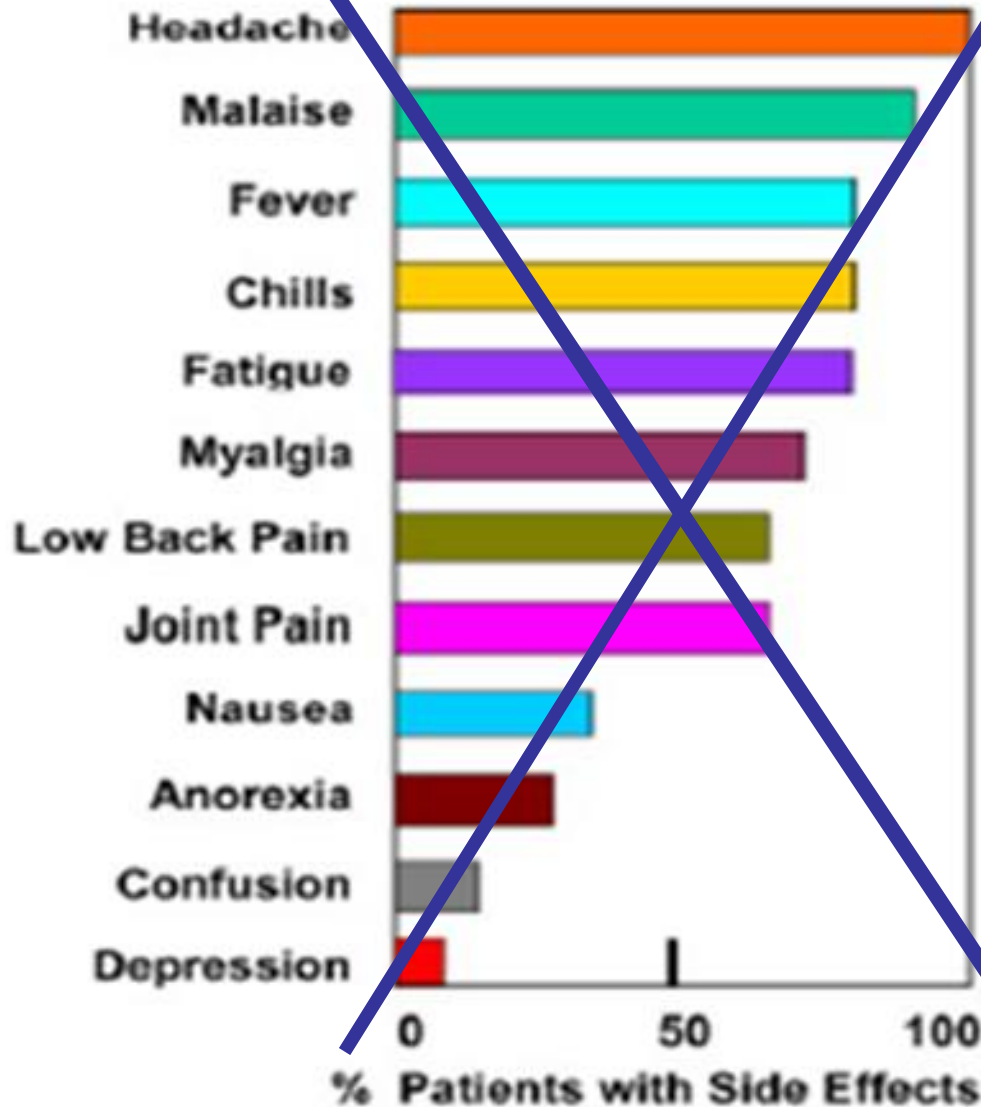
DALIAH

A Danish Study of Low-Dose Interferon-alpha2
versus Hydroxyurea in Ph-Negative
Myeloproliferative Cancer

A National Multicenter Study on The Efficacy, Toxicity and QoL

Target
200 Patients

Side Effects of Interferon



Use Low Dose :

Pegasys 45 ug x 1 sc/week

PegIntron 30 ug x 1 sc/week

10-20 % side effects

Interferon Intolerability

&

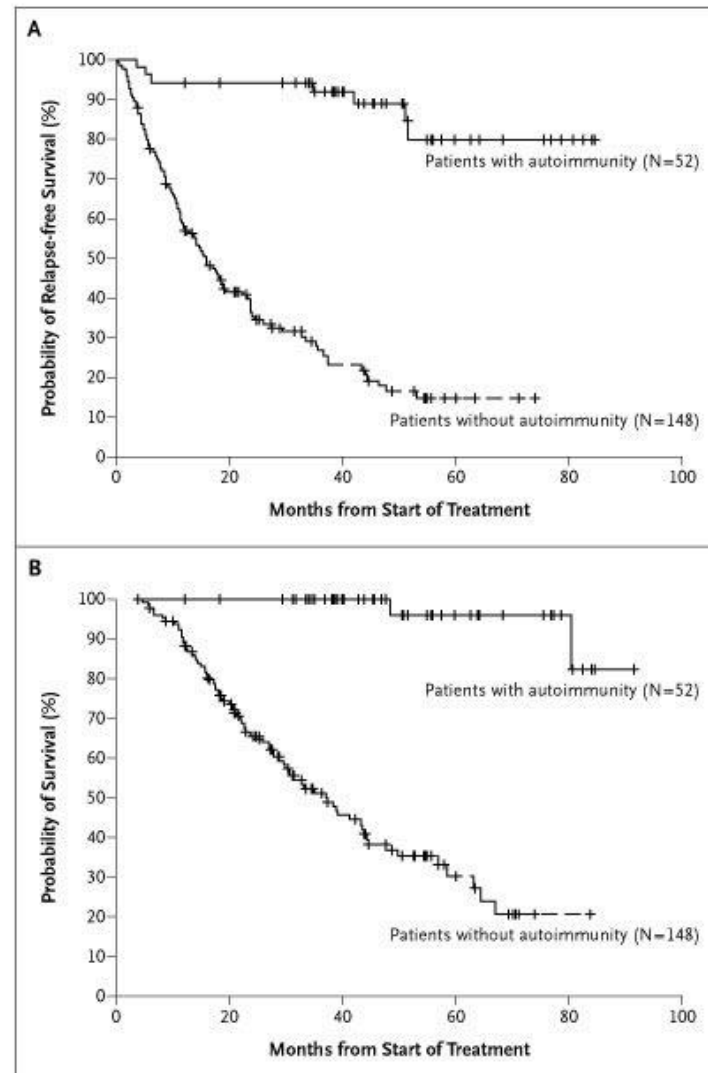
Interferon Resistance

Toxicity – Side Effects - Autoimmunity

Response Patterns

- the subgroup of patients with severe side effects (drop out) - a better and more rapid reponse to IFN ?
- The subgroup of patients with autoimmunity during treatment with IFN – a better and more rapid response to IFN ?

Prognostic Significance of Autoimmunity during Treatment with Interferon ?



Gogas H et al.
N Engl J Med 2006; 354:709

Combination Therapy

**Interferon Alpha2 + JAK Inhibitor
in Polycythemia Vera and Myelofibrosis**



Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Case report

Combination therapy with interferon and JAK1-2 inhibitor is feasible: Proof of concept with rapid reduction in JAK2V617F-allele burden in polycythemia vera

M.E. Bjørn^{a,*}, K. de Stricker^b, L. Kjær^a, K. Ellemann^c, H.C. Hasselbalch^a^a Department of Hematology, Roskilde University Hospital, Køgevej 7-13, 4000 Roskilde, Denmark^b Department of Pathology, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense, Denmark^c Department of Neurology, Roskilde University Hospital, Køgevej 7-13, 4000 Roskilde, Denmark

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Interferon
Ruxolitinib

ABSTRACT

We report a 55 year old woman with post-ET PV for 12 years, who experienced resolution of severe constitutional symptoms within 3 days, a marked reduction in splenomegaly and a rapid decline in the JAK2V617F allele burden during combination therapy with interferon-alpha2a and ruxolitinib. Within 4 weeks the patient achieved complete hematological remission with normalization of peripheral blood counts and within 10 months the JAK2V617F-allele burden was reduced from 90% to 28%. Such a rapid decline in the JAK2V617F allele burden is highly unusual in PV-patients during low-dose IFN-alpha2 monotherapy and this finding warrants a prospective study with combination therapy.

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Figure 1. Hemoglobin, leukocyte and platelet levels during combination therapy with Ruxolitinib and Peg-IFN-alpha2a.

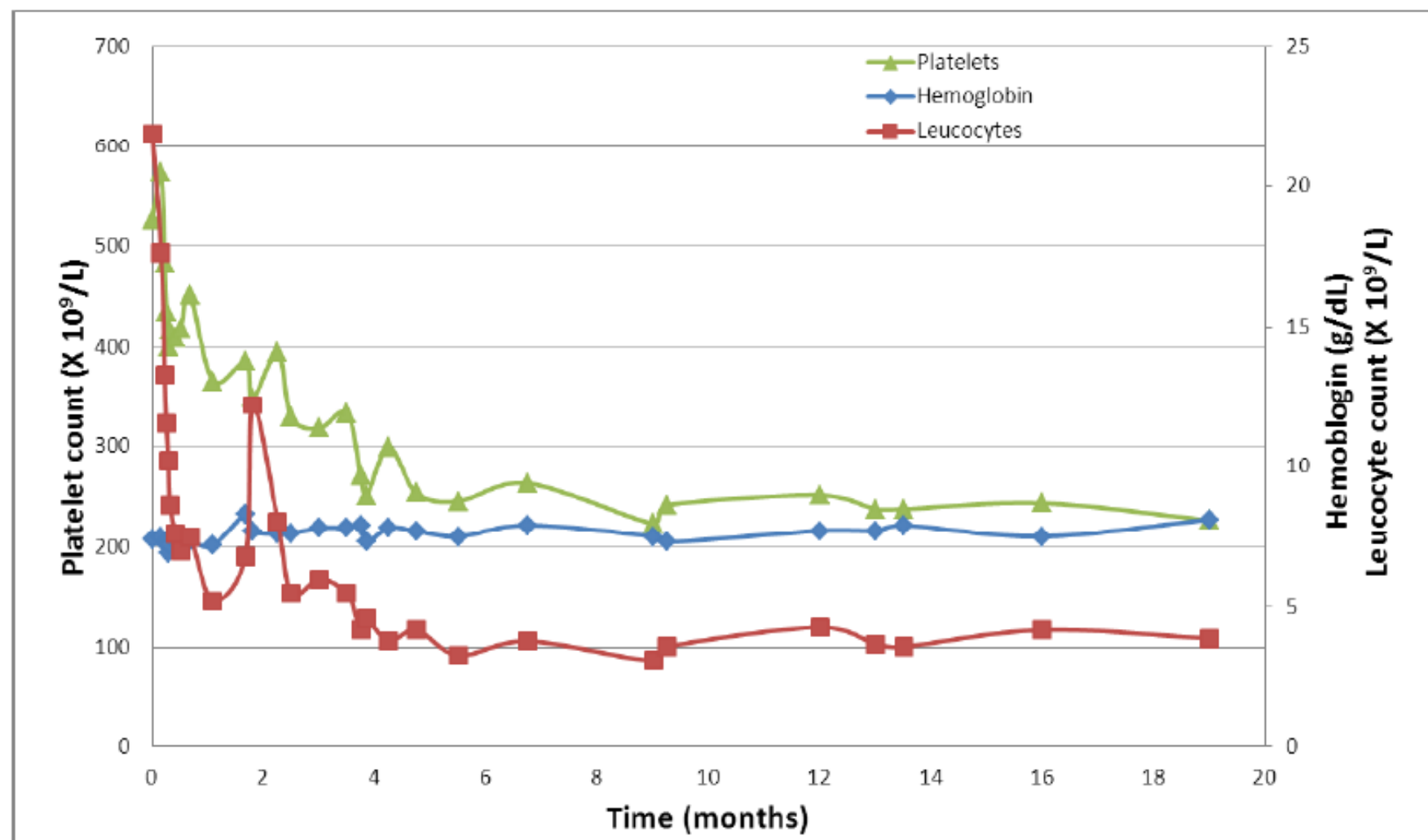
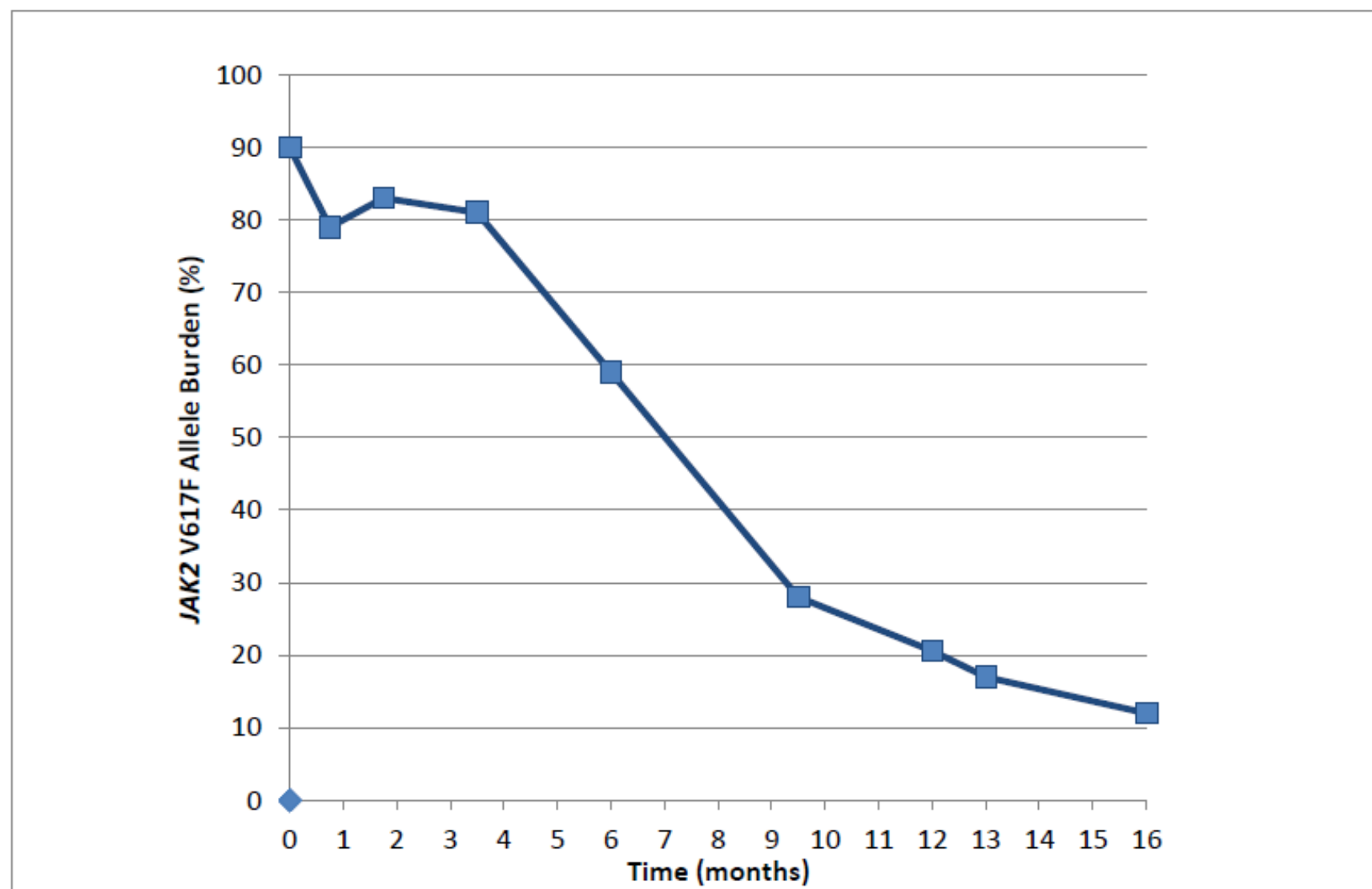


Figure 2. *JAK2* V617F allele burden over time.



Oxidative stress inhibits IFN- α -induced antiviral gene expression by blocking the JAK–STAT pathway

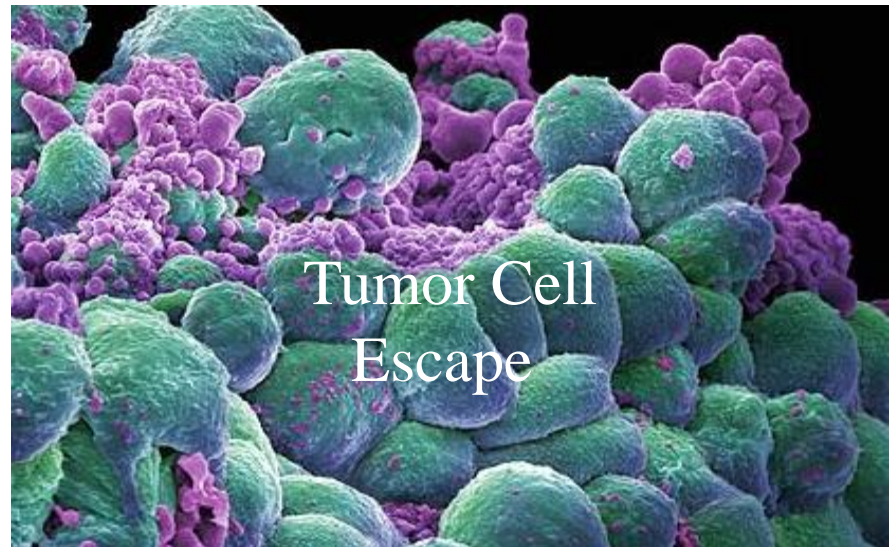
Danilo Di Bona^{1,2,*}, Marco Cippitelli^{3,4}, Cinzia Fionda^{3,4,†}, Calogero Cammà^{1,2},
Anna Licata¹, Angela Santoni^{3,4}, Antonio Craxì¹

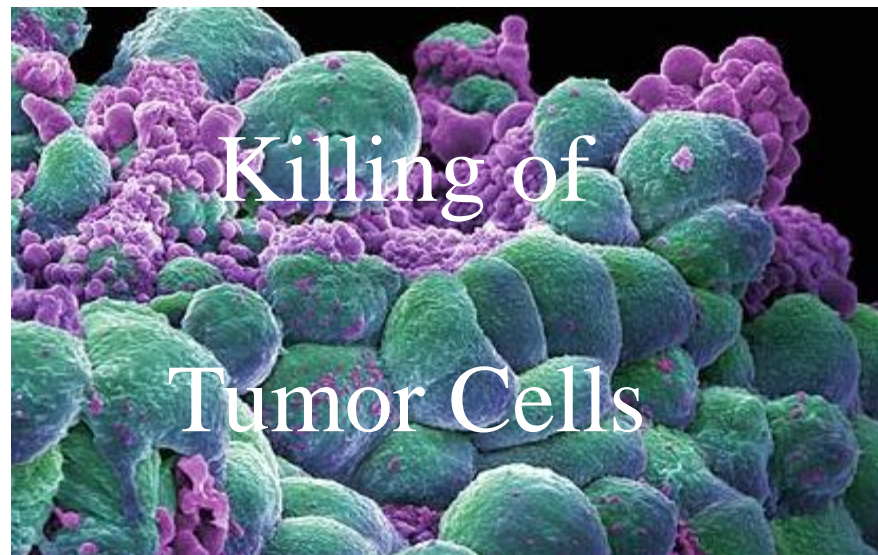
¹*Cattedra e Unità Operativa di Gastroenterologia, Dipartimento Biomedico e di Medicina Specialistica, University of Palermo, Palermo, Italy*

²*IBIM, Consiglio Nazionale delle Ricerche, Palermo, Italy*

³*Department of Experimental Medicine and Pathology, Istituto Pasteur-Fondazione Cenci Bolognetti, University 'La Sapienza', Rome, Italy*

⁴*Regina Elena Cancer Institute, Rome, Italy*





JAK1-2 Inhibition + Statins

Quelling the Fire

The Inflamed Bone Marrow



Statins and Anti-inflammation

- Inhibit leukocyte activation
- Inhibit platelet activation
- Inhibit release of pro-inflammatory cytokines (eg. IL-6, TNF-alfa)

Statins inhibit JAK2V617F-dependent cell growth

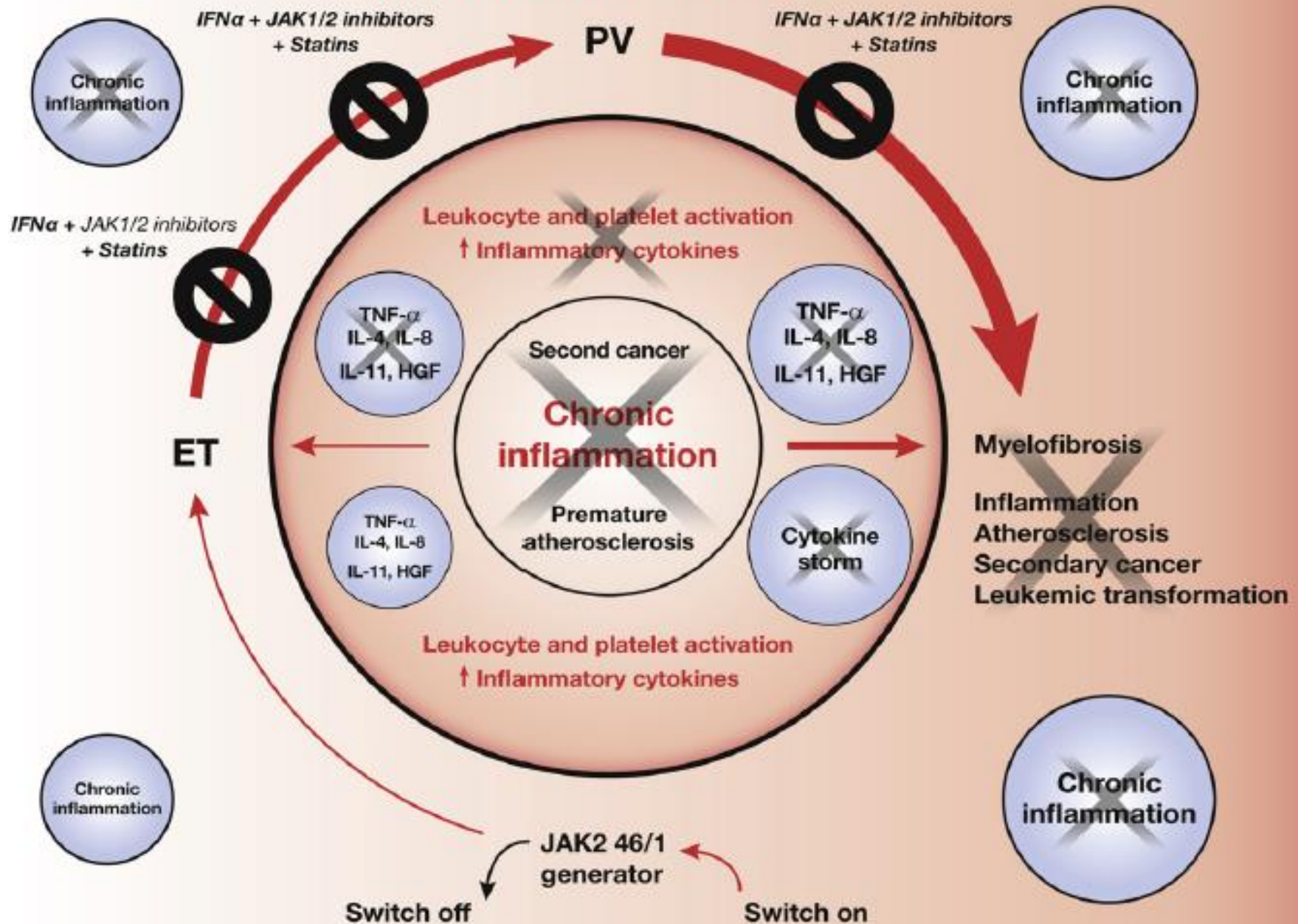
Statins enhance JAK2 inhibition

Combination Therapy

Interferon Alpha2 + Ruxolitinib + Statin



MPN Inflammation Model



HGF: hepatocyte growth factor; IL: interleukin; TNF: tumour necrosis factor

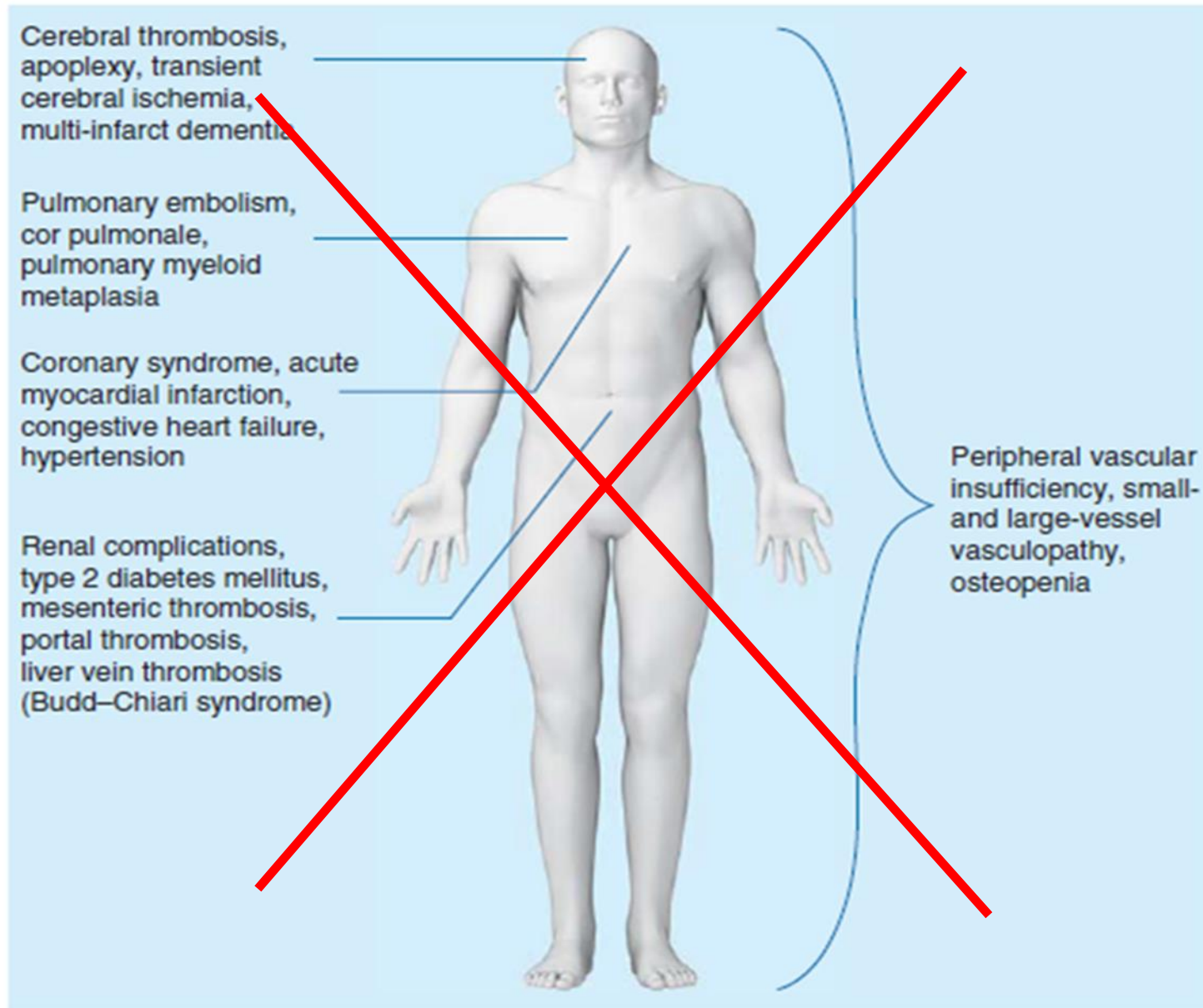
The Fairytale on Interferon-Alpha2 in The Treatment of Polycythemia Vera and Related Neoplasms.

Is the Ugly Duckling becoming the Beautiful Swan
only by The Randomized Trial ?



The Ugly Duckling . A Fairy Tale by Hans Christian Andersen

~~Chronic Inflammation Premature Atherosclerosis Cancer~~

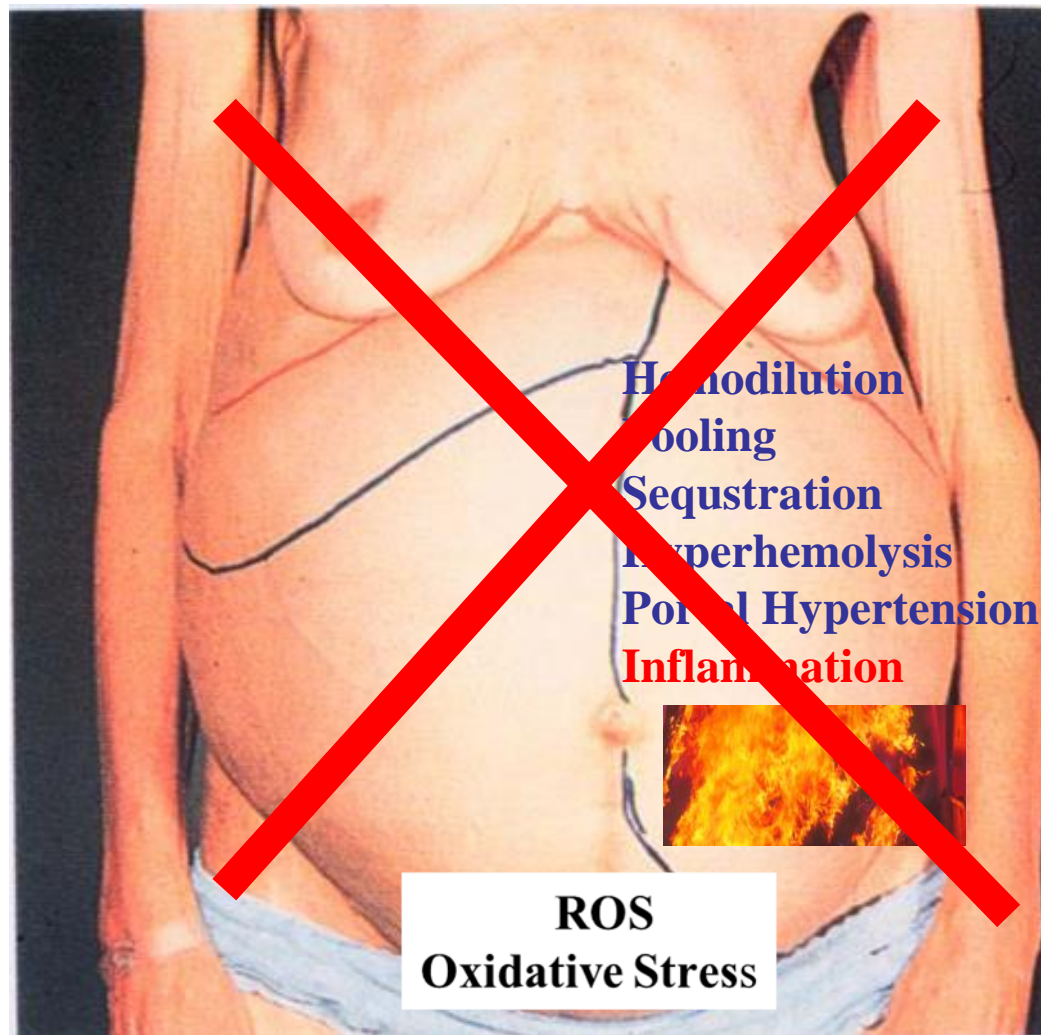


The Inflamed Bone Marrow



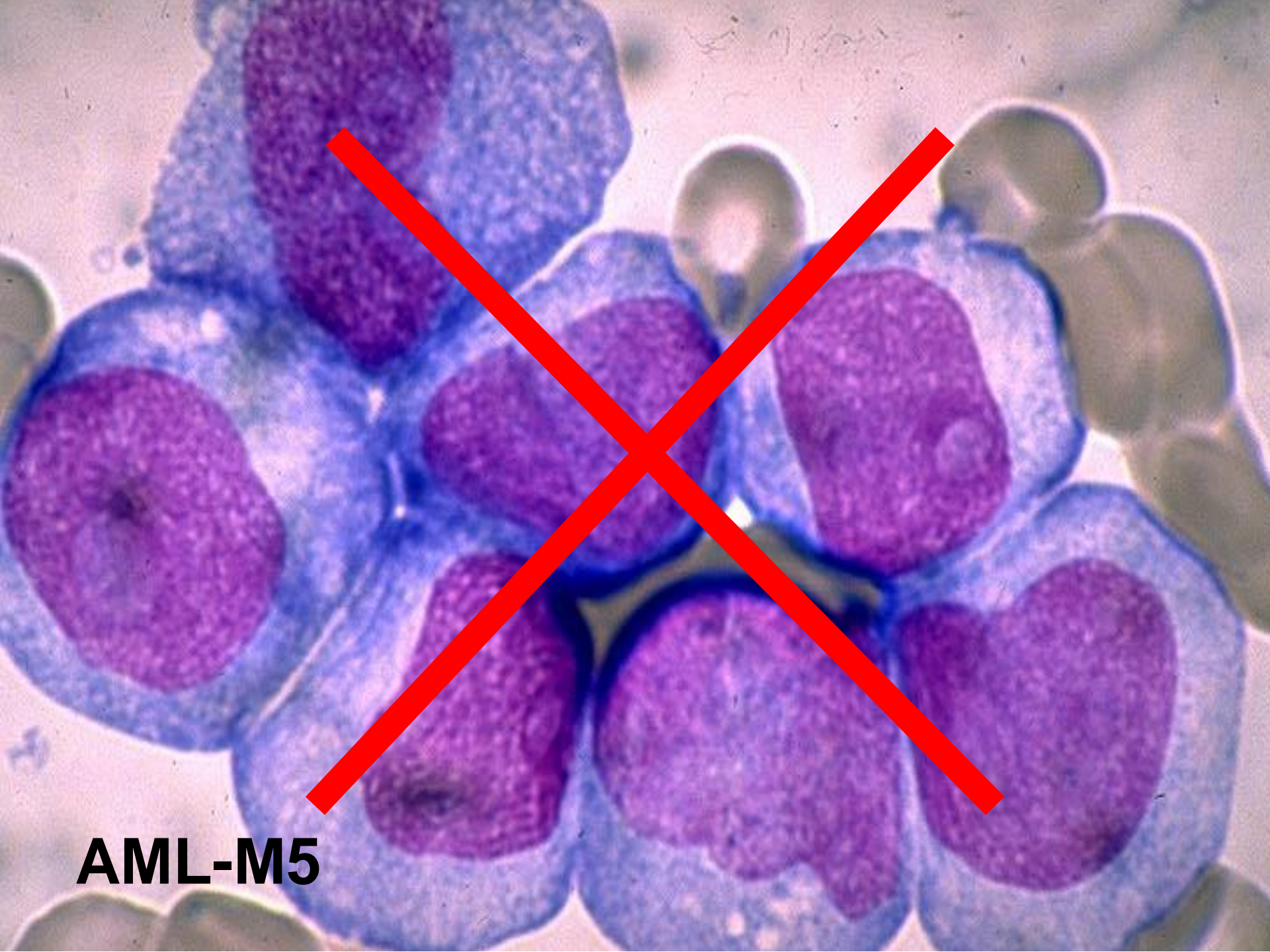
The chicks are flying prematurely (escaping) from the burning nest

ROS
Oxidative Stress



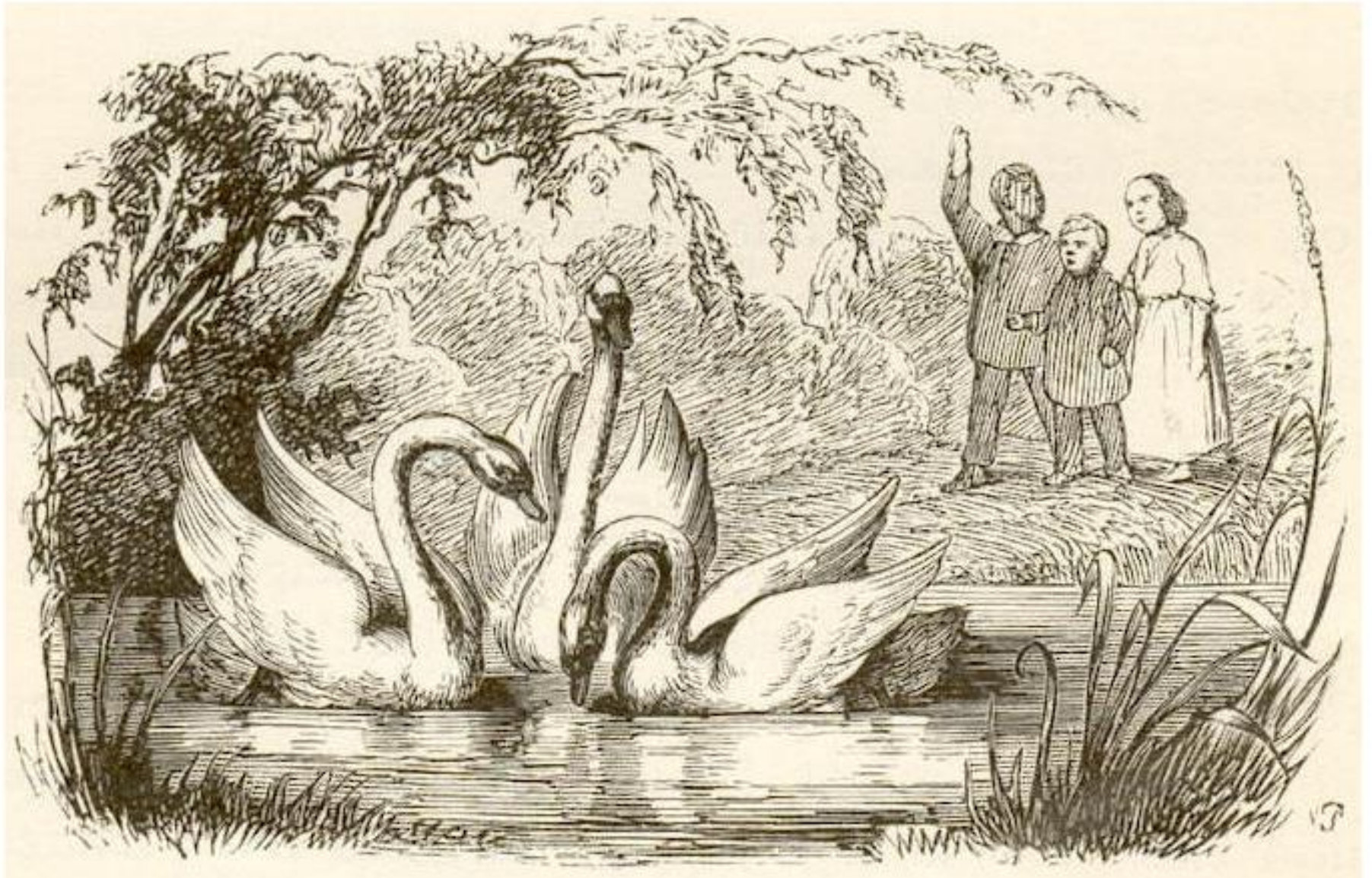
Myelofibrosis with huge splenomegaly

Anemia: bone marrow failure, hemodilution, pooling, sequestration, hyperhemolysis, portal hypertension, bleeding



AML-M5

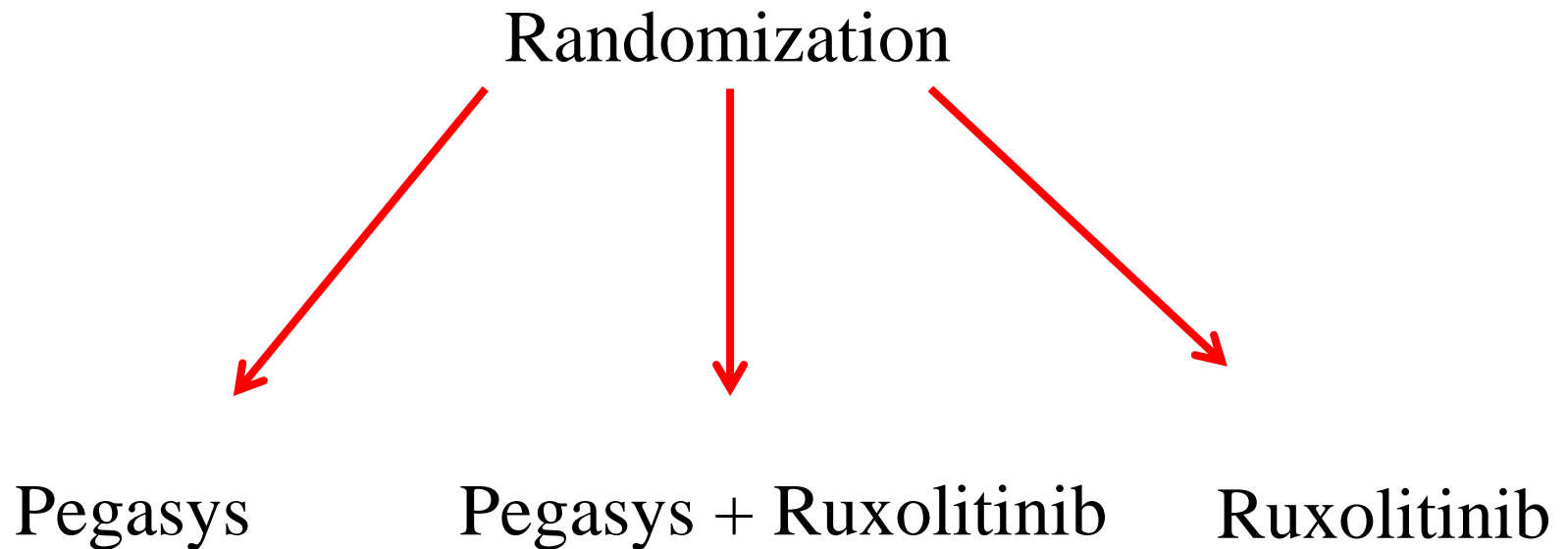
**Combination Therapy Interferon-alpha2 + Ruxolitinib
The Beautiful Swan Becoming Even More Beautiful ?**



The Ugly Duckling . A Fairy Tale by Hans Christian Andersen

The Dream Stream Study

Newly Diagnosed PV and Hyperproliferative MF



Hans Christian Andersen



Photograph taken by [Thora Hallager](#), 1869

Born	2 April 1805 Odense, Funen, Denmark
Died	4 August 1875 (aged 70) Copenhagen, Denmark
Occupation	Writer
Language	Danish
Nationality	Danish
Genre	Children's literature , travelogue

Signature

Handwritten signature of Hans Christian Andersen.













A low-angle photograph looking up at several tall, mature pine trees. The trees have thick, brown trunks and dense, green needle-covered branches that fill most of the frame. The sky is a clear, bright blue, visible through the gaps in the foliage. The lighting suggests a sunny day, with some highlights on the leaves and shadows within the canopy.

The Future Looks Bright

A scenic view of a beach with waves, a small boat, and people in the water under a blue sky. The text "Thank you for your attention" is overlaid in red.

**Thank you for
your attention**